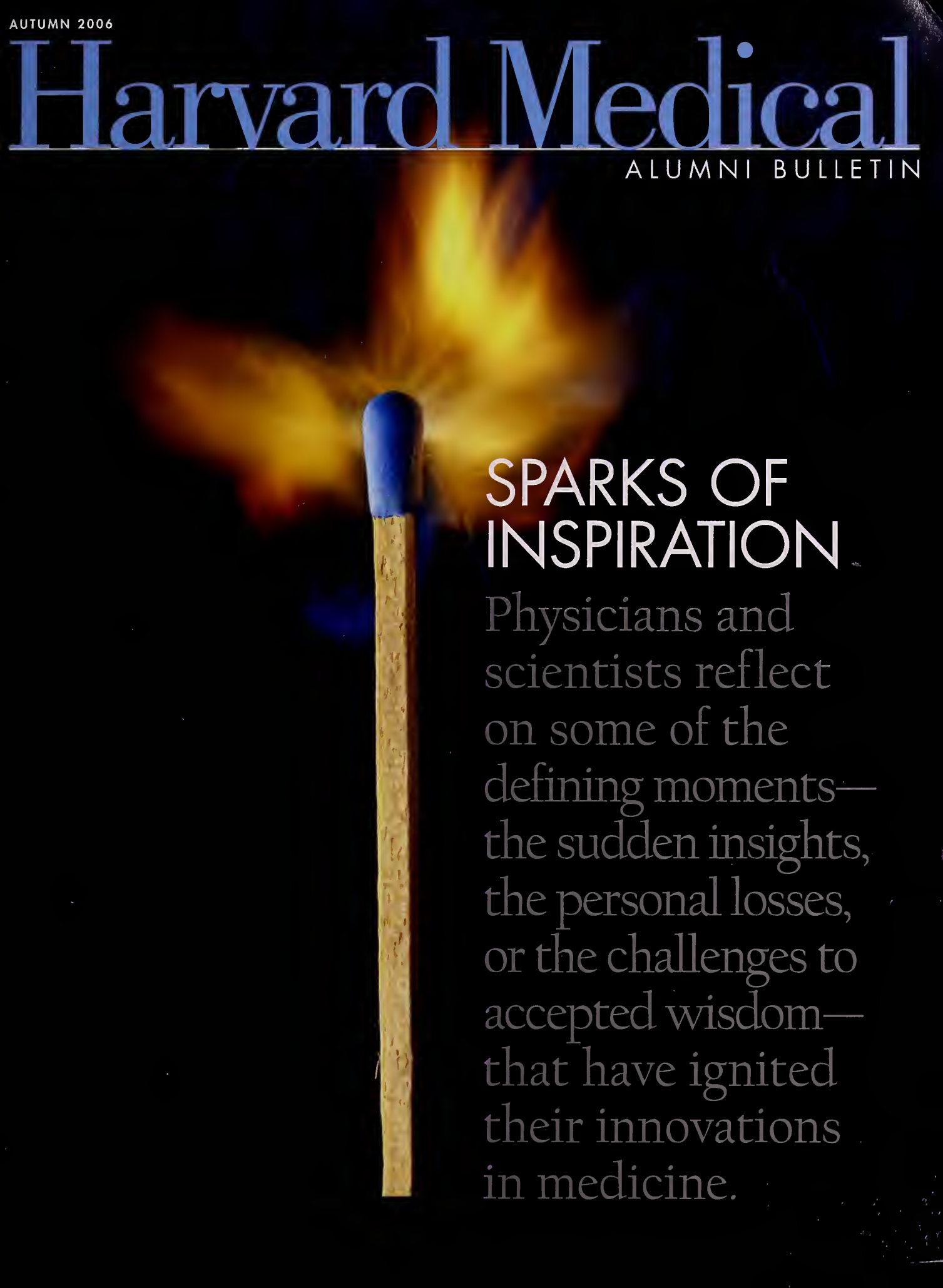
AUTUMN 2006

Harvard Medical

ALUMNI BULLETIN



SPARKS OF INSPIRATION

Physicians and scientists reflect on some of the defining moments—the sudden insights, the personal losses, or the challenges to accepted wisdom—that have ignited their innovations in medicine.

CHAMPIONS

1906

During the September 1906 opening of Harvard Medical School's original Quadrangle, H. P. Bowditch (left), Class of 1868, and J. Collins Warren, Class of 1866, took a moment to survey a photograph of an outdoor tea held on the new campus. Ceremonially enrobed, each received an honorary doctorate of laws for his work in raising funds for the School's sixth home, a marble marvel now a century old.

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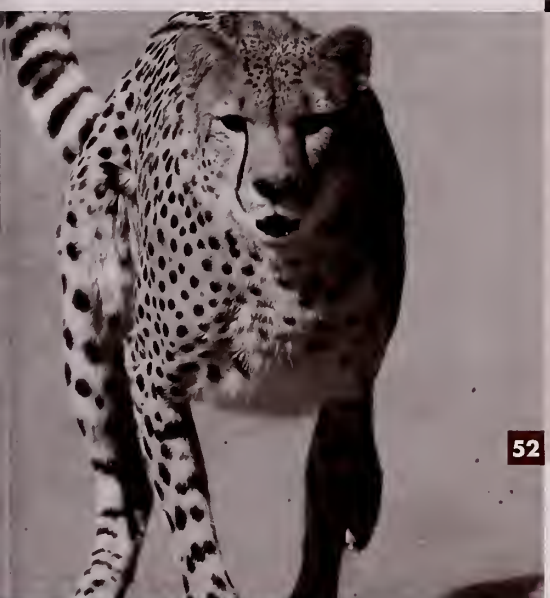

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Harvard Medical
ALUMNI BULLETIN

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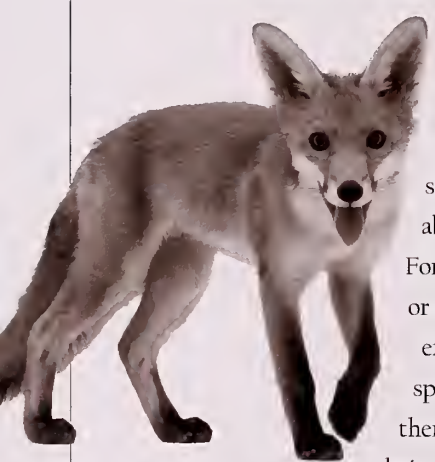
In This Issue

THIS ISSUE OF THE *BULLETIN* IS, IN ITS WAY, A MEDITATION ON THE relationship of hedgehog and fox in medicine. "The fox knows many things, but the hedgehog knows one big thing," wrote Archilochos 26 centuries ago. A mercenary soldier and an angry man, he was also a poet, one whose work survives only in fragments. This short line—in translation three syllables short of a haiku—sounds self-evident for a millisecond and then is utterly mysterious. I suppose the poet could have been writing about animal behavior, but that seems improbable; military strategy was more likely his topic. The most satisfying interpretation, however, is that human thinkers come in two species, or so Isaiah Berlin argued in his essay "The Hedgehog and the Fox."

The fox attends to the world as it presents itself. The fox is short on preconception, long on observation. An aerial view of its itinerary shows a scramble of paths and purposes, inquiry and distractions. Hedgehogs, by contrast, are committed to "a single, universal, organizing principle in terms of which alone all that they are and say has significance." Successful careers in science often belong to the hedgehogs, people with a centripetal disposition and singleness of mind who pull data into a system. Viewed from high above, their work is as legible and coherent as a crop circle. (Medical practice, on the other hand, often calls for a fox-like willingness to follow each scent where it leads, to pursue a mental life that is, on the whole, centrifugal.)



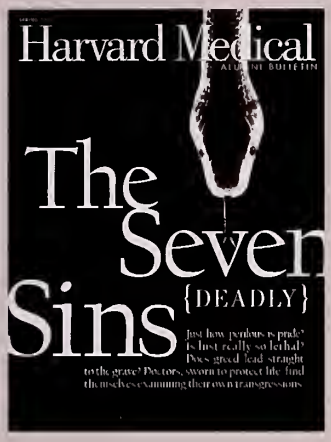
For the special report in this issue, we asked seven alumni or faculty members at HMS to tell us about the moment when they became hedgehogs. For each of them, at a certain point an important idea or principle took hold and became the focus of their experience and aspirations. In retrospect, they spent a little time as hedgehogs in foxes' clothing but then settled down to the single-minded business of their careers. That, at least, is one reading of their stories. An alternative interpretation is that they went through a metamorphosis, switching species when events made it clear to them what their path would be. We leave it to our readers to discern which hypothesis of discovery and change best fits the evidence of these lives.

William Ira Bennett

PHOTO: JANE BURTON/DORLING KINDERSLEY/GETTY IMAGES

STRUCTURAL DEFECTS

I greatly appreciated the insight and humor of the Spring 2006 issue on the seven deadly sins. Just prior to my time at HMS, I was steeped in thoughts of sin while attending the Union Theological Seminary in New York City.



Union is a bastion of liberation theology. On the subject of sin, liberation theology shifts the focus away from the individual and holds that much of sin is *structural.* It is embedded in power and privilege and is woven into the very fabric of our societies and institutions.

A good example of structural sin comes at the beginning of the piece Atul Gawande '94 wrote on greed. His department chair sets out the formula for salaries in surgery: "The job, he explained, came with a guaranteed salary for three years. After that, I would be on my own: I'd make what I brought in from my patients and would pay my own expenses."

This eat-what-you-kill approach has powerful and detrimental ramifications. It strongly discourages providing care for a "poor payer mix." In other words, faculty members who care for medically underserved patients pay the price in terms of lower compensation because their patients are not considered as valuable.

If we doctors truly want to face our own sins and address health care inequities, we need to examine the systems we control. It's not just about governmental policy or insurance companies. It's about us.

KATHERINE JAHNIGE MATHEWS '94
ST. LOUIS, MISSOURI

Pay It Forward

In the excellent article by Atul Gawande '94 in the spring issue of the *Bulletin* he cites a surgeon with an annual net income of $1.2 million who believes that doctors need to understand that they are businessmen and—presumably—should charge what the traffic will bear. It is worth reminding this physician and others who might be attracted to that philosophy that U.S. taxpayers likely helped finance their entry into the "business." Perhaps up to half the costs of education and training through medical school and residency is subsidized by the federal and state governments. Not a bad deal—someone else makes the investment and you reap the reward. I have long held that medical students should have the opportunity to turn down government subsidies, but that, if they take them, they do so with the understanding that, in their future practices of medicine, they will not discriminate against people without insurance or those covered by Medicaid and Medicare. This would provide a better "business" model than that suggested by the physician who extols the "free-enterprise" model.

RASHI FEIN, MD
BOSTON, MASSACHUSETTS

Dressed for Success

I read the Spring 2006 issue of the *Bulletin* cover to cover and enjoyed it, as I do every issue.

The article on the "deadly sin" of physician pride—"Vanity Fare," by Perri Klass '86—reminded me of my days as a third-year medical student doing a core clerkship in surgery at Massachusetts General Hospital. That was when I first noticed that attire seemed to reflect hierarchy. Male medical students, interns, and junior residents wore white pants, white collarless shirts, and short white jackets; senior residents tended to wear white pants, shirts and ties, and short white jackets; the chief resident wore dress slacks, a shirt and tie, and a short white jacket; and the professors wore dress slacks, shirts and ties, and long white lab coats. Imagine the boost to my pride when I started my dermatology residency at UCLA and learned that I would be wearing a long white lab coat. Perhaps, I thought proudly, some "civilians" passing me in the hallway might mistake me for a really young professor!

In his piece on lust ("Lust Me, I'm a Doctor"), Stephen Bergman '73 states, "In the bizarre American calculus, the

lust for a thong can nearly bring down a commander in chief...." I presume Dr. Bergman is referring to the *perjury* that resulted from that lust and that led to the impeachment of a commander in chief, his suspension from the Arkansas bar, payment of a $25,000 fine to the Arkansas Bar Association, and suspension and subsequent resignation from the U.S. Supreme Court bar. As to "...but the lust for oil and empire and revenge that strews bloodied bodies in its wake," perhaps Dr. Bergman may be sublimating some lust in the form of poetic hyperbole.

MASSAD GREGORY JOSEPH '77
SOUTH PASADENA, CALIFORNIA

The Skinny on Fat

William Bennett '68, perhaps motivated by a desire to relieve the obese of their guilt, makes the case that we have little or no control over whether we become obese ("Gorged on Guilt" in the Spring 2006 issue of the *Bulletin*), and all evidence to the contrary is brushed aside. For example, choosing a life of vigorous exercise—or choosing to prepare one's own food in reasonable portions from vegetables, lean protein, whole grains, and healthy fats—receives mention only in an admission that genetic destiny is "modified by environmental influences."

The ease with which we modify our environment, of course, sets us apart from all other organisms, and I have yet to meet an individual determined to maintain a healthy body weight who mysteriously ended up needing a gastric bypass. American culture heavily advertises oversized portions of energy-dense foods at low cost and places insufficient emphasis on exercise. Not surprisingly, the prevalence of obesity is rising. It seems much more likely that these facts are related than that genetics is solely to blame, especially when Americans are becoming substantially more obese in a matter of decades and the prevalence of diabetes is rising, and when it is easy to watch the impact of a Western lifestyle on immigrant populations.

In addition, if Dr. Bennett is going to promote a culture free of judgment, was it appropriate to compare the South Beach Diet, which was developed as a medical treatment for coronary artery disease, to a concentration camp? Is fighting heart disease really as bad as the Holocaust?

Genetic makeup and environmental exposures influence our propensity to abuse alcohol. Yet, we expect people to make an effort to overcome alcoholism, whether the task is difficult or not, and we also know that patients at risk of alcoholism can avoid the danger entirely by choosing to abstain from the drinking that their peers indulge in without consequence. Doctors can and should approach obese or at-risk patients with the compassionate and nonjudgmental expectation that they try to improve their lifestyles. Creating a culture in which obesity "just happens" means that we give the obese and at-risk populations our condolences rather than an action plan, depriving them of their very real, if not complete, control over their diet, exercise, weight, and health.

IAN JENKINS, MD
SAN DIEGO, CALIFORNIA

Brittle White Lies

I enjoy the *Bulletin* and read most of each issue. As much as I enjoyed the seven deadly sins edition, one feature unrelated to the special report—the "Night of Reckoning" by Kim-Son Nguyen '07—contained what I consider an ethically questionable "pearl" that deserves comment. The author tells a patient with abdominal pain, acute symptoms, and an alarming abdominal CT that she does not have appendicitis and will not require emergency surgery. He seems to feel that this "white lie" somehow provided at least a temporary solution to the problem. Yet who benefited from this dissimulation? The patient? Or Mr. Nguyen?

In more than 30 years in clinical and academic radiology, I have seldom seen a situation that this strategy has improved. I have witnessed, however, several situations where such temporary relief (for the house officer) has led to patient disillusion, anger, and resentment brought

PHOTO: ARCHIVE HOLDINGS, INC./THE IMAGE BANK/GETTY IMAGES

THROUGH A GLASS DARKLY

On page 13 of the Spring 2006 issue is a picture of a man using a microscope. Is the picture a joke, or did the user really not understand that he had the scope turned backward and his hand possibly interfering with the light source and mirror? Also the lens seems to be up too high. Is this a real photo or a poorly contrived picture? *[Editor's note: The photo is an archival image from a stock photo agency.]*

Thank you, by the way, for the page on my ancestor Langdon Frothingham, who graduated from the Harvard School of Veterinary Medicine's class of 1889.

TOM FROTHINGHAM '51
DURHAM, NORTH CAROLINA

about by similar efforts on the part of young physicians trying to escape the difficult task of dealing with a patient truthfully. Although the late William McDermott '42 would occasionally use the "We won't have to operate" line with great success in dealing with the families of hopeless cases, I never recall him or any of my other HMS mentors suggesting being less than truthful with patients.

I would recommend that the next time Mr. Nguyen encounters a similar situation (and he will, if he stays in the clinic), he simply admit to the patient that he has to talk her case over with his team rather than giving himself an easy out with an ethically questionable "answer" to her question. Mr. Nguyen's temporization should not be emulated.

JAMES A. NELSON '65
SEATTLE, WASHINGTON

Hat Trick

On the inside front cover of the Spring 2006 issue of the *Bulletin* is a lovely old photograph from Children's Hospital Boston. The brief caption contains some inaccurate information, however. Children's Hospital Boston was indeed established in 1869, but not in the home of one of its founders, Francis Henry Brown, Class of 1861. Instead, the original building was a townhouse—now nonexistent—on Rutland Street in Boston's South End, only a short walk from Dr. Brown's home on Waltham Street.

I would also like to point out that the individual pictured with the young patient is a second-year nursing student. This is apparent from the two thin black stripes on her cap, which would have been replaced by a single thick one upon graduation.

Those who wish to see more wonderful old photos can refer to a small book printed last year by Arcadia Publishing, *Images of America: Children's Hospital Boston.*

MARK A. ROCKOFF, MD
CHAIR, ARCHIVES COMMITTEE
CHILDREN'S HOSPITAL BOSTON
BOSTON, MASSACHUSETTS

PHOTO COURTESY OF THE ARCHIVES OF CHILDREN'S HOSPITAL BOSTON

Caps and Gowns

Thank you for reprinting the great picture of the Children's Hospital nurse and her droopy-drawered patient. Those uniforms, though not as beautiful as those worn by the nurses at Massachusetts General Hospital or Peter Bent Brigham Hospital, were worn proudly, even with the black stockings. I married one of those "square hats" (Virginia Codington), and we had four wonderful sons who recently came to see me in my 95th year.

One of the good things about being my age is the absence of all the sins that you so graphically outlined in your spring issue. There is still joy, however, in being part of a great profession—and in being able to read about it in the *Bulletin.* Keep it up!

HENRY WORK '37
BETHESDA, MARYLAND

The Bulletin *welcomes letters to the editor. Please send letters by mail* (Harvard Medical Alumni Bulletin, *25 Shattuck Street, Boston, Massachusetts 02115); fax (617-384-8901); or email (bulletin@hms.harvard.edu). Letters may be edited for length or clarity.*

One Hundred Years of Science

WHEN HARVARD MEDICAL SCHOOL'S original Quadrangle was dedicated a century ago, HMS researchers were about to unveil a method for measuring the chemical compounds in blood samples. In celebrating the centennial of that dedication, HMS recently sponsored symposia that looked toward the contributions its researchers would make during the next century of scientific discovery.

In the opening symposium on neuroscience, HMS dean Joseph Martin noted that four big questions drive the field: How do cells work together so the brain can function as it does? How can a brain be repaired or cured following injury or disease? What makes us different from one another? How do brains adapt to the changing world?

Sensory neuroscience offers some clues. "Our problem is to understand how objects in the world are interpreted by specialized cells in organs and how information is processed by the brain," said Rachel Wilson, HMS assistant professor of neurobiology. Wilson's studies of the olfactory circuit of fruit flies suggest a model of cross-talk and amplified signals that enable the olfactory system to better differentiate among odors as information travels up to the brain, where it might activate behaviors to eat or flee or fight or mate.

David Anderson, the Roger W. Sperry Professor of Biology at the California Institute of Technology, has literally bottled the smell of "fly fear" in experiments to understand the circuitry of how genes act to help the animal react and survive aversive stimuli. By combining the tools of systems neuroscience and molecular genetics, Anderson and collaborators have identified one component—carbon dioxide—and part of the sensory neuronal circuit necessary for avoidance behavior. But another elusive component is also needed to activate the neurons.

Similarly, in hearing, key details of the transition between sensing and perceiving are evading persistent inquiry. Using laser tweezers, Howard Hughes investigator David Corey, HMS professor of neurobiology, and his colleagues can measure the tiny mechanical forces at the tips of mouse hair cells, named for the bundle of stiff cilia that sway in unison at specific frequencies. The researchers have found that links between the tips of neighboring cilia can open and close calcium channels with sufficient force to turn the mechanical stimulus of a sound wave into an electrical signal the brain can recognize. The protein that makes up the channel itself remains a mystery.

In zebra finches, Allison Doupe '79, a professor of psychiatry and physiology at the University of California, San Francisco, is assessing auditory motor-control areas. She noted that a brain region vital to helping zebra finches learn their scratchy songs seems to allow adults to switch between producing precise songs for an audience and testing new tunes when the birds sing alone. That same brain region may govern the babbling of children trying to mimic their parents.

"The last century was the century of the gene and cracking the genetic code," said HMS neurobiology chair Carla Shatz. "This new millennium is the millennium of the mind: If we know our brains, we really will know ourselves."

The Microbes Are Coming

When it comes to self-knowledge, bacteria may hold the key, said Dennis Kasper, director of the Channing Lab at HMS and Brigham and Women's Hospital. "The striking fact about the normal microbial colonization of mammalian bodies," he said, "is that the

number of bacterial cells outnumber host cells by 100 to one."

Kasper's group has been studying the biological effects of polysaccharides made by a bacterial species in the gut. In harmful bacterial infections, these long-chain sugar molecules are known as virulence factors. But in colonization by beneficial bacteria, they may help maintain the host's health.

The rapid accumulation of basic research advances is fueling the scientific response to potentially dangerous new pathogens, said Michael Farzan, assistant professor of microbiology and molecular genetics at HMS. Only eight months after the World Health Organization issued a global health alert for the SARS virus, Farzan's group published the identity of the viral receptor.

Farzan notes that technological advances from work on HIV, the Human Genome Project, mass spectroscopy, and protein identification algorithms support the modern detection work essential to understanding the mechanisms of viral entry and the development of new ways to fight infections.

Don Ganem '76, professor of microbiology/immunology and medicine at the University of California, San Francisco, made a strong case for gathering plenty of old-fashioned epidemiological evidence, developing tight clinical case definitions, and using critical thinking in a program of new pathogenic discovery. "If you look hard enough for microorganisms," he said, "you will find them."

Genomics and Medicine

New genomic strategies and tools took center stage in the final symposium on cancer and drug design. Researchers at Jackson Laboratory in Bar Harbor, Maine, have developed a new systems genetics approach to create mouse models of common diseases in humans and to study the essential nature of mammalian chromosomes, said Richard Woychik, director of the Jackson Laboratory.

Joan Brugge, chair of the HMS Department of Cell Biology, is using a three-dimensional culture system to model alterations in the architecture of glandlike structures in the breast caused by genes implicated in breast cancer.

"The three-dimensional structure allows us to distinguish the biological activities of genes not distinguishable in cells cultured as monolayers in a Petri dish," she said. The models resemble the various histologies of breast cancer and can be used to test the effects of chemotherapy agents.

Stephen Elledge, the Gregor Mendel Professor of Genetics and Medicine at HMS, has generated a large database of proteins phosphorylated in vivo during DNA damage. He has used the database to identify proteins that may play a role in cancer. Some of the usual suspects have appeared, as well as new players in DNA replication and recombination, the cell cycle, cellular assembly and organization, cell death, and RNA post-translational modification.

One company has adapted the high-throughput approach to structural biology. Stephen Burley '87, chief scientific officer at SGX Pharmaceuticals, described a drug-discovery process that uses a dedicated beam line at the Advanced Photon Source in Chicago for x-ray crystallographic screening of drug fragments to find new protein kinase inhibitors and other oncology targets. Clinical testing for one such compound in people with chronic myelogenous leukemia is expected to begin in 2007. ■

Carol Cruzan Morton is a science writer for Focus.

The Class of 2010

IN SEPTEMBER HARVARD MEDICAL SCHOOL WELCOMED THE 166 members of its Class of 2010 in the traditional manner: by holding a White Coat Ceremony. New white coats were worn by graduates from 65 different undergraduate institutions in 32 states and Puerto Rico, as well as from schools in Canada, Ghana, Jamaica, New Zealand, Serbia and Montenegro, Thailand, Trinidad and Tobago, and the United Kingdom. Twenty-eight percent of the students are Asian Americans, 11 percent are African Americans, and nearly 4 percent are Latinos. Native Americans make up less than 1 percent. Fifty-three percent of the incoming group is female and the group's ages range from 21 to 34. ■

PHOTO: LIZA GREEN

The State of the School

JOSEPH MARTIN, DEAN OF HMS, described his ninth annual State of the School speech as his most poignant one, having recently announced his intention to step down from his position in July. During his talk he outlined the seven priorities he had developed early on to help continue the School's growth. He also reviewed what the HMS community has accomplished and what more needs to be done.

Martin's first priority was expanding the basic science programs. He noted the creation of the new Department of Systems Biology, the Harvard Institute of Proteomics, the Program in Chemical Biology, and the New England Regional Center of Excellence for Biodefense and Emerging Infectious Diseases. In addition, the neurobiology and cell biology groups have both expanded and taken advantage of interinstitutional collaborations.

Martin's second priority was improving hospital relationships. At the time of his arrival the recent hospital consolidations had created an atmosphere of competition rather than cooperation. Martin established seed grants that led to Quad-based and hospital-based faculty collaborations. The Dana–Farber/Harvard Cancer Center, for example—which has received the largest federal comprehensive cancer center grant ever—involves more than 800 researchers from across the HMS community.

The dean's third priority was to nurture education. He instituted new ways of rewarding teaching. The Academy at HMS, devoted to improving medical education, has been key to enhancing the teaching skills of the faculty. The first class to experience the new integrated curriculum arrived on campus in August. The first of their courses, a two-week introductory class, ended in a standing ovation.

Martin's fourth priority was to develop community and public service opportunities for students. A service requirement is now a part of the new curriculum.

The fifth priority was to take advantage of technology to improve communications and access to resources. Martin noted that the School has made great gains in its research computing cluster, making technologies available for data-intensive research.

When introducing his sixth priority, Martin said, "The diversity issue, in many ways, has been the most challenging." An early system-wide review of junior faculty "stuck" in the lower ranks has since resulted in many women and minorities receiving promotions.

In discussing his final priority, Martin outlined several grants and gifts the School has received in the past decade, but conceded that the task of fundraising is never done.

Martin concluded by pointing out the addition of the word "diverse" to the HMS mission statement, which now truly reflects his early goals for the School. ■

Leaving the Helm

PHOTO: STEVE GILBERT

JOSEPH MARTIN, WHO HAS SERVED AS DEAN of HMS for more than nine years, has announced his plan to step down in July 2007. Until then, he will focus on such key priorities as education reform, science planning, and faculty recruitments.

Martin, a neurologist and neuroscientist by training and the former chief of the neurology service at Massachusetts General Hospital, was recruited to HMS from the University of California, San Francisco, where he served as dean of the medical school and then chancellor of the UCSF system. Martin has been known as a bridge builder and champion of interdisciplinary science.

When Martin steps down, he will focus his attention on the efforts of the Harvard Center for Neurodegeneration and Repair, which links more than 700 neuroscientists across all the Harvard-affiliated institutions in an effort to find new therapies for disorders such as Alzheimer's, Parkinson's, and other neurodegenerative diseases. Derek Bok, interim president of Harvard, has convened a faculty advisory committee to begin the search process for a new dean, with the expectation that the ultimate selection will be made by the next president of Harvard.

"Joe Martin has served Harvard Medical School and the University with integrity, imagination, and great distinction," Bok said. "His successor will inherit a School that is exceptionally strong in terms of medical education, scientific research, and connection to the clinical enterprise." ■

Nominations Sought

AFTER NEARLY A DECADE OF DEVOTED service, Tenley Albright '61 has stepped down as chair of the HMS Alumni Fund. To nominate yourself or another HMS graduate to take on this role, email the interim chair, Daniel Federman '53, at: daniel_federman@hms.harvard.edu.

Ties That Bind

WHEN HARVARD MEDICAL SCHOOL'S GRADUATES CROSS the stage each year, they receive not only a diploma, but also the School's commitment to support and sustain them as physicians throughout the years to come. The importance of this commitment—and the bond it forges—has grown increasingly well defined during our recent Alumni Council meetings.

The HMS alumni office, which has completed a major reorganization, is now well poised to offer additional benefits to graduates. Under the leadership of George Thibault '69, director of alumni relations, and Mary Moran Perry, executive director of alumni relations, the office has conjured new synergies and expanded resources.

The most notable of these resources are now in development: an electronic directory of HMS alumni and a reinvigorated Harvard Medical Alumni Association website. These advances will give new support to the Association's efforts to stay in touch and to encourage you to do the same—both high priorities for the Council. With these links to Harvard Medical School, we will be collectively and individually only keystrokes away from connecting with the School's resources. The website in particular promises to be a wonderful boon to reunion planning and to provide a portal through which communication on issues, plans, proposals, and news can pass.

With these links to Harvard Medical School, we will be collectively and individually only keystrokes away from connecting to the School's resources.

Several Council members have pledged to work with William Chin '72, the Council's first president-elect, on how we can best exploit the website's potential to enhance ties among HMS alumni. Steven Weinberger '73, the second president-elect, will lead another group of Council members as they focus on ways to bring students and alumni together, actually and virtually, using the website. Council members Susan Okie '78 and Rodney Taylor '95 have a head start in this area: They have organized a group of alumni in Baltimore and Washington, DC, who are ready to work with fourth-year students looking for training opportunities in that region.

Council members are also looking for new ways alumni might use the School's continuing medical education resources. We are working with Sanjiv Chopra, faculty dean for continuing education, to establish opportunities for HMS graduates to take advantage of the School's myriad offerings. One outcome of this outreach is that HMS alumni have a standing invitation to be guest attendees at the regional courses titled "Current Clinical Issues in Primary Care," or Pri-Med. Embodied in these courses are presentations of broad medical interest, such as the recent one on RNA interference by Craig Mello, recipient of this year's Nobel Prize in Medicine.

All this activity has not, however, caused us to lose momentum on an issue many of us consider vital—helping to alleviate student debt. During his recent term as Council president, Steven Schroeder '64 directed our attention to the problem of excessive student indebtedness and urged Dean Joseph Martin to consider steps to ameliorate this burden. Many of you have already acted; the 2005–06 Alumni Fund raised additional dollars that were dedicated to defraying debt.

This activity comes at a critical juncture; after nearly a decade of exemplary service, Tenley Albright '61 has stepped down as chair of the HMS Alumni Fund. The interim chair, Daniel Federman '53, however, will carry the banner for the program while the search for a new Alumni Fund chair is under way.

During the past several years the Council has renewed its vigor and sense of mission for the challenges the School faces. We want to do more than receive reports on the state of the School and its various activities from administrative and faculty leaders. We want to assist the HMS community and to represent you. Please help us do both by bringing your ideas and concerns to our attention. ■

A. W. Karchmer '64 is chief of the Division of Infectious Disease at the Beth Israel Deaconess Medical Center in Boston. He can be reached at akarchme@bidmc.harvard.edu.

For more information about the Harvard Medical Alumni Association, visit www.hms.harvard.edu/alumni.

PHOTO: LAURENT HAMELS/PHOTOALTO

Prescriptions for Hope

MY FATHER ENCOUNTERED THE FIRST OF THE PHYSICIANS in 1941. As the youngest and only unmarried sibling of eight Bursztajns, my father, Abraham, had been left in charge of the family's lumberyards in Lodz soon after the German invasion of Poland on September 1, 1939. Most of the members of his family had left for Warsaw, which had been something of a haven during World War I. My father, not having other family responsibilities, volunteered for the dangerous job of overseeing the family's holdings in what was considered an area far more likely to be involved in the fighting.

The Nazis had compiled a list of prominent Jewish families with assets, and my father's family was on that list. In 1941 the Nazis captured him, threw him in jail, and tortured him to reveal his family's whereabouts. He refused.

"One of us will die, but it will be me," the physician told my father. "I do not have any way of treating you, but you are young. If you don't give up hope, you will survive."

After a particularly severe flogging, my father fainted. He was surprised to awaken in the jail's infirmary. His interrogators, intent on making him disclose his family's location, had decided to keep him alive for continued questioning—and torture. As he stirred, he realized that standing before him was a doctor, himself a Jewish prisoner, who ministered to the other prisoners. "I will die here," my father told the older man.

"One of us will, but it will be me," the physician replied. "I do not have any way of treating you, but you are young. If you don't give up hope, you will survive."

This physician inspired my father by first acknowledging their shared hopelessness but then instilling in him a determination to survive. My father did his part and survived. When he eventually returned to what was by then the Lodz Ghetto, he was offered a "choice" job—to collaborate with the Nazis by becoming a Jewish police officer. His refusal enraged the Nazi-installed figurehead of the ghetto, Mordechai Chaim Rumkowski, known among those in the ghetto as the King of the Jews. Rumkowski slapped my father, then sought to humiliate him by assigning him to work on sewage disposal.

Remembering the doctor's words, my father resolved to transform the job into a way to create hope. His first priority was to establish a home for a Jewish Resistance cell. He found willing members among some of his sewerage co-workers, and he recruited others by pulling acquaintances off the train platform as they were waiting to embark for Auschwitz. One of the people he recognized was Miriam, the daughter of a furniture craftsman he knew from his family's lumber trade.

Miriam had given up hope after her father's death from starvation, and she was already on the train, knapsack on her back. But when my father talked with her, she agreed to his plan. My father approached the Nazi officer supervising the deportation. "She is one of the sanitation workers who has been ordered to stay in the ghetto until the last," he said. "She needs to come with me." When the officer looked skeptical, my father played his final card: He flashed a family photograph given to him by a high-ranking German officer with anti-Nazi leanings. The officer in charge let Miriam go.

Running for Cover

By 1944 my father and the other members of the Resistance cell were convinced the Nazis were planning to kill those who remained in the Lodz Ghetto. But the resistors had no weapons with which to mount a revolt, and by that time they had heard of the carnage suffered by those living in the Warsaw Ghetto during its 1943 uprising. After much debate, they decided to resist by going into hiding. But where? The Nazis had been employing dogs to sniff out other Resistance hiding places. My father realized that the sewer system itself, if waterproofed areas could be created, offered a natural hiding place. The stench of the sewers would confuse the dogs.

The challenge was obtaining the cement necessary to build a watertight bunker in the sewer system. The only available cement was in a well-secured Nazi warehouse outside the ghetto walls. My father and one of his comrades decided to risk a night raid.

The raid was an initial success. While carrying 100-pound bags of cement back to the ghetto, however, my father and his colleague were shot at, and a Nazi patrol gave chase. Zigzagging at a sprint, my father evaded the automatic weapons fire until a bullet struck him in the shin. Injured and bleeding profusely, he could no longer run. With the enemy closing in, he looked for a refuge. He spotted a nearby dumpster and, still

PHOTO KAREN BEARD/PHOTOGRAPHER'S CHOICE/GETTY IMAGES

IN MEMORIAM: Visitors stand in the doorway of a Holocaust memorial in Lodz, Poland, erected on the site of the Radegast train station, which was used as a point of embarkation for Jews on their way to the death camps. Through quick thinking, the author's father was able to rescue his future wife just before the doors closed on a train bound for Auschwitz.

clutching his bag of cement, jumped in, pulling the cover over him. The Nazi patrol rushed past.

When the area cleared, my father staggered with the heavy bag back to the Resistance's rendezvous. Now that the cement had been saved, he needed to save himself. Surely that morning the Nazis would investigate, notice the blood on the bridge, and look for absentees from the morning's work detail to interrogate as suspects in the raid. My father's comrades contacted one of the few doctors still left in the shrinking ghetto.

In the hours before dawn, the doctor risked his life to visit my father. He no longer had surgical instruments, so he straightened a coat hanger to fashion a crude probe. Sterilizing it as best he could, he used the makeshift tool to extract the bullet. He had little time, and few words were exchanged. In the absence of anesthesia, afterward the surgeon gripped my father's shoulders with affection to help quiet the searing pain. When they parted, my father kissed the hands that had saved him. That morning my father was able to appear for the roll call with a baggy pair of pants hiding the dressing on his wound.

Working at night, the members of the Resistance cell used the precious cement to construct a bunker in the sewer system. Concealed by water, the bunker had pipes that brought in air, water, and electricity. For the final six months of the Nazi reign of terror, 14 people hid in that space—and survived. By then, my father had helped spread the word about the sewer system, and many others found shelter there or used it as an entryway into the basements of abandoned houses.

The Gift of Life

My father could not save his family of origin. But he and his comrades in the Resistance cell, including Miriam—who later became his wife and my mother—did save the lives of others. The memories of his family, of his comrades in the Resistance, and of the physicians who had saved his life had become hope-sustaining assets that neither the Nazi terror nor the passage of time could obliterate.

The Lodz Ghetto was liquidated in August 1944, and for each night after, as he emerged from the bunker to forage for food, my father felt as if the dead were keeping watch. Finally, the living, in the form of the Russian Army, came to the rescue. The soldiers found more than 800 Jewish survivors of the ghetto holding on in the sewer system.

My father never saw either physician again. Decades later, his eyes would fill with tears when he recounted learning that the doctor who had removed his bullet had been found in hiding in the evacuated ghetto and was murdered along with his family.

Beyond carrying personal meaning for me, my father's story of survival has resonated with me professionally. It reminds me that physician integrity can be maintained in the most trying situations. If the physicians my father encountered during the Holocaust could preserve the decency of authentic doctoring, then so can we all, whatever the circumstances. Supporting our patients' hope and autonomy—even in the most resource-limited conditions and against all odds—is our fundamental duty, even when we face with them the most hopeless of realities. ■

Harold J. Bursztajn '76 is an HMS associate clinical professor of psychiatry at Beth Israel Deaconess Medical Center and a co-founder of the Program in Psychiatry and the Law at Harvard Medical School. As a child in Lodz, he remembers people rushing up to his father to thank him for saving their lives. (The author's original essay appeared in the Winter 1996 issue of The Journal of Clinical Ethics. *This adaptation appears with permission of the journal, which retains rights.)*

PHOTO KATARINA STOLTZ/REUTERS/CORBIS

The Mind Has Mountains

Reflections on Society and Psychiatry, by Paul R. McHugh '56
(Johns Hopkins University Press, 2006)

MAYBE YOU'VE HEARD ABOUT THE MENTAL HOSPITAL THAT BUILT separate elevators for its neuropsychiatrists and its psychoanalysts because they refused to ride together. Someone described the elevator solution to me during my first psychiatric rotation. The notion made a deep impression, although I later learned, to my disappointment, that those doppelgänger elevators do not exist. But this much is true: Those who enter a field about human nature also enter a field divided by human nature.

Paul McHugh '56, professor of psychiatry emeritus at the Johns Hopkins University School of Medicine, has been thinking for many years about psychiatry's problems—including this kind of sectarianism—and its solutions. He is a cantankerous, intelligent writer, so precise that he names each tiny ligament before transecting it. He dissects clearly, confidently, and down to the bone.

The Mind Has Mountains is a compilation of his essays (which are themselves compilations from his teaching and clinical experiences) from *Commentary, The Weekly Standard, The American Scholar,* the *New England Journal of Medicine,* and other worthy publications. The chapter titles are proclamations, such as "Psychotherapy Awry," "How Psychiatry Lost Its Way," "Romancing Depression," and "The Death of Freud and the Rebirth of Psychiatry." The premise is stern: Psychiatrists have "made claims that were not true, pressed for attitudes and behaviors that were destructive, and held beliefs about human mental life that were incredible." The conclusion is dire: "When caught up by the social suppositions of their time, psychiatrists can do much harm."

How have we become forces of such destruction? Partly it is because we are only human. "Psychotherapists," McHugh explains, "have a natural tendency to give themselves over to the softer virtues of kindness, gentleness, and soothing support...at the expense of the sterner virtues of truth, responsibility, and justice." Partly it is because of hubris; we don't discourage the world from believing we alone "know deep secrets...[that] tend to turn on matters sexual [and] unconscious." There is also our vulnerability to shoddy and faddish social thought. Since the days of Freud, instead of the rigorous differential diagnosing found in other fields, "the romanticist tendency in psychotherapy is to rely upon feelings for evidence, on metaphors for reality, on inspiration and myth for guidance."

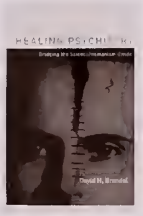
McHugh's essays are full of critical examples, such as adult attention deficit disorder, gender identity disorders, social phobias, repressed memories, and multiple personality disorder (he lances and drains that last one as if it were filled with pus). Even the *Diagnostic and Statistical Manual of Mental Disorders,* with its Chinese menu of symptoms, comes under his scalpel. Diagnosis driven only by appearances and symptoms is "so crude as to foster inept educational programs and clumsy clinical practices."

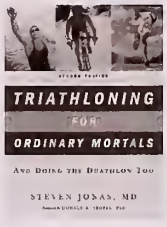
So, what is left of the body after all this dissecting is done? Good news for psychiatry: McHugh reports that with proper reconstructive efforts, the organs scattered here and there can be reassembled. Four decisive and different ways of formulating patients must be part of any psychiatric education; to the author's mind, they will redeem the field. Brief summations cannot do justice to the richness of his disease, dimensional, behavior, and life-story perspectives. I wish I had learned them years ago. Together, he writes, they constitute a method of differential diagnosis—and therefore treatment—free of bias and as close to "empirical psychiatric principles" as is humanly possible. Medical education owes this to the psychiatrist, and the psychiatrist owes it to the patient. It is the least we can do for patients—and the most.

This is a book full of certainty. There is not a single confused thought in it. Yet it may bring up confusing feelings. The reader races through the first 150 pages driven—sometimes flogged on—by its fierce arguments. But the certainty is not always pleasant to hear, particularly in the last sections, when it extends into areas of ethics and politics. After finishing McHugh's pronouncements on do-not-resuscitate orders, living wills ("signposts of our own culture of death"), and the "just war" he finds in Iraq, I found myself missing some of those "softer virtues of kindness, gentleness, and soothing support." An even more liberal reader may find himself wishing to ride in a separate elevator. Ethics and politics come to roost in our own little homes, and we who share the profession may live on very different streets. ■

Elissa Ely '88 is a psychiatrist at the Massachusetts Mental Health Center.

PHOTO: PHOTODISC PHOTOGRAPHY



When Invisible Children Sing

by Chi Huang '97 with Irwin Tang *(Salt River Books, 2006)*

The book describes Huang's education in compassion and hope, gained while treating orphans and street children in La Paz, Bolivia. He meets child prostitutes like Mercedes, a sexually abused 15-year-old who cuts herself; the infant Maria, who dies in a hospital because neither her mother nor the hospital can afford to feed her; and Alejandro, who leaves the orphanage to become a successful chef.

Healing Psychiatry

Bridging the Science/Humanism Divide, by David H. Brendel '95 *(MIT Press, 2006)*

The author proposes a clinical pragmatism to mental health care, one that synthesizes its scientific and humanistic aspects. He argues that psychiatrists must learn to consider the process of diagnosis to become more responsive to the consequences of that diagnosis. Drawing on case studies and the work of thinkers such as William James, Class of 1869, and contemporary bioethicists, Brendel calls for an open-minded, yet scientifically informed approach to understanding mental disorders.

Moral Values, Politics & You

The Moral and Tribal Nature of All Politics, by Fidel Davila '76 *(MoDaus Publishing, 2006)*

All politics begins with personal values and how they shape an individual's moral philosophy and ethics, according to the author. He also discusses how the sharing of personal and moral values forms "tribes" of people and explains the roles of such tribes in politics. Included are essays on the ethics of abortion, marriage, end-of-life directives, and lying.

The Psychopathy of Everyday Life

How Antisocial Personality Disorder Affects All of Us, by Martin Kantor '58 *(Praeger Publishers, 2006)*

This book makes the case for the existence of "mild psychopathy" in individuals whose behavior falls somewhere between normal and psychopathic. Kantor calls them the "forgotten people of psychopathology." They appear to be upright citizens marred by a smidgen of dishonesty, but they really have a treatable, mild psychopathy. The author outlines underlying personality structures and explains how traditional therapy can be tweaked for effective treatment.

Global Burden of Disease and Risk Factors

Edited by Alan D. Lopez, Colin D. Mathers, Majid Ezzati, Dean T. Jamison, and Christopher J. L. Murray '91 *(Oxford University Press and the World Bank, 2006)*

One of the more useful components of this reference text is the section containing more than 100 pages of charts that show how risk factors complicate disease and influence mortality rates in comparative age and geographic groups. Those charts compare, for instance, how obesity affects breast cancer, heart disease, and osteoarthritis among Europeans, South Asians, and several other populations across eight age cohorts. The editors also include analyses of the data.

Triathloning for Ordinary Mortals

And Doing the Duathlon Too, by Steven Jonas '62 *(third edition, W. W. Norton, 2006)*

Recreational runners, cyclists, and swimmers hoping to enter long-distance races can turn to the pages of this book for training guidelines and suggestions for choosing appropriate races. Jonas himself didn't do a triathlon until he was 46, and he now provides tips and inspiration for getting started and finishing healthily and happily.

Adolescent Medicine

An Issue of Primary Care: Clinics in Office Practice, edited by Donald E. Greydanus and Victor C. Strasburger '75 *(Saunders, 2006)*

The editors begin their book by taking the long view of adolescence—analyzing its Latin and Greek roots, reflecting on the first teen health clinic in the United States, and considering issues facing today's 55 million young people. Contributors guide readers in 15 specific areas of concern for contemporary youth, including sexuality and reproductive health, violent behavior, media influence, sports injuries, substance abuse, and diabetes management.

Heavy Weather

THEY WERE CALLED NERVE STORMS, these explosive, incapacitating headaches. The "megrims" brought debilitating pain before wringing themselves from their victims through nausea and vomiting. And, according to nineteenth-century practitioners, they always began with an aura, a term covering such omnibus symptoms as zigzagging light flashes, tunnel vision, and other unsettling distortions of sensory information.

Although mentioned in works from the time of Hippocrates, migraines and their symptoms were first described fully in the late 1870s. By the early 1940s, the distinct personalities of the migraine and the aura were better known: For one thing, it was understood that "sick headaches" could occur without auras.

In the July 19 issue of the *Journal of the American Medical Association*, researchers at Brigham and Women's Hospital added to medicine's knowledge of nerve storms by showing that women who suffer from migraines with auras have a higher risk for cardiovascular disease.

Migraines are described as periodic neurovascular disorders that repeat throughout the lives of their victims. Often, they are marked by headaches so severe the sufferer becomes temporarily incapacitated. For some, the pain is accompanied by an aura. In the United States, in any given year, approximately 18 percent of women and 6 percent of men suffer migraines, percentages that represent an estimated 28 million people.

Previous studies of women's risk for ischemic stroke and cardiovascular disorders hinted at links between these conditions and the incidence of migraines, especially migraines with auras. In their study, the scientists at Brigham and Women's sought to probe for possible connections between migraines and stroke and coronary events.

The scientists used data collected from participants in the Women's Health Study, which tested whether the use of low-dose aspirin and vitamin E had any preventive effect on cardiovascular disease in women who were at least 45 years old. At the start of the study, the 27,840 participants were judged to be free of angina and cardiovascular disease. Enrolled between 1992 and 1995, the women in the study were followed for ten years.

The researchers analyzed the study data and found that slightly more than 5,000 participants had a history of migraine headache. Within this pool of

PHOTO TOM & DEE ANN MCCARTHY/CORBIS

migraine sufferers, 3,610 had reported active migraines; that is, they had experienced a migraine in the past year. Of the women with active migraines, 1,434 also had reported auras.

When the investigators compared data from women who did not report a history of migraines with those from women who suffered from migraines with auras, they found that women in the latter group were twofold more likely to experience a major cardiovascular event, myocardial infarction, ischemic stroke, death due to ischemic stroke, or angina. They also found that this increase in risk was not constant; it seemed to spike into being around the six-year point.

For women who had migraines but no auras, the study's conclusions were more favorable. Such women showed no increase in their risk for experiencing a cardiovascular event.

Although the researchers cannot say precisely why women who suffer these tempests of light and pain have an increased risk for major cardiovascular events, they speculate that underlying biological mechanisms believed to raise the risk of cardiovascular problems—such as high cholesterol, high blood pressure, and other artery-narrowing conditions, and possibly even the genetic differences linked with elevated homocysteine levels—may act in a concerted manner to increase a woman's risk over time.

For women who do experience auras when they have migraines, lead author Tobias Kurth, an HMS assistant professor of medicine in Brigham and Women's preventive medicine unit, cautions that further research is needed to better understand the relationship between migraines with auras and an increased risk for major cardiovascular events. But, while these women wait for such research, Kurth suggests they be alert for ways to control their risk, such as by exercising, eating plenty of fruits and vegetables, maintaining a healthy weight, and refraining from smoking. ■

Children's Digest

WEIGHTY ISSUE

Tip-the-scales fot or just baby fot? A study in the July issue of *Obesity* indicotes it's likely to be the former. A research group led by Motthew Gillmon, on HMS ossociote professor of ombulotory core ond prevention, sifted 22 yeors of doto gothered during well-child visits of 120,000 eostern Mossochusetts children under two yeors of oge ond discovered thot the prevolence of overweight children increosed 59 percent during the two decades. The proportion of children ot risk for becoming overweight jumped 30 percent. Infonts fored even worse: The number of pudgy infonts increased 74 percent ond those ot risk of becoming so increosed 59 percent. The scientists soy the problem likely storts before birth; compared to their 1980s peers, pregnont women todoy weigh more ond goin more during pregnoncy.

BRINGING UP BABY

Move over Vegomeotovitomin. Omegaven is not only less of a mouthful, it may octuolly be on elixir, ot leost for tiny tykes with troubled tummies. A triol by reseorchers ot Children's Hospitol Boston found thot infonts who require porenteral nutrition ore better served by o preporotion contoining omego-3 fotty ocids thon by the usuol mixture thot relies on soy ond other plant oils. Their use of an omego-3–rich product, Omegaven, for two infonts who hod intestinol problems ot birth completely reversed cholestosis in eoch—one even wos oble to be removed from the list of liver tronsplonts hopefuls. The study's teom leoder wos Mork Puder, on HMS ossistont professor of surgery. The report oppeors in the July issue of *Pediatrics*.

SAFE SLUMBERS

An investigation into sudden infont deoth syndrome (SIDS) hos fingered o biologicol suspect: obnormolities in the broinstem's serotonin system. The findings help exploin why mole infonts and infants under six months of oge ore more likely to succumb to such o deoth. They olso offer the hope thot o diagnostic test—possibly even o treatment—could be developed. In the United Stotes, SIDS is the leoding couse of deoth ofter the newborn period.

Between 1997 ond 2005, o team of researchers from Children's Hospitol Boston ond HMS studied the medulloe oblongoto token during outopsies of 41 infants. The medullo oblongoto, which forms the lower portion of the broinstem, is home to nerve cells thot produce the neurotronsmitter serotonin. The chemicol is thought to control such homeostotic functions os breathing, blood pressure, ond sensitivity to corbon dioxide, o buildup of which couses suffocotion.

When the scientists onolyzed tissue from the 31 infonts who had died from SIDS ond the ten control infonts who hod died ocute deoths from other couses, they found the medulloe from SIDS infonts—especiolly in the boys—were deficient in o porticulor serotonin receptor ond in o tronsport protein thot "recycles" serotonin. And although these medulloe showed an obnormolly high number of serotonin-producing neurons, most serotonergic neurons were immoture.

The reseorchers note thot such defects could mor an infont's obility to control the vitol homeostatic functions ruled by serotonin. The report oppeored in the November 1 issue of the *Journol of the Americon Medicol Associotion*.

PHOTO: INGRAM PUBLISHING/GETTY IMAGES

Red Red Wine

Recent research at HMS has conjured up images of tiny paws grasping the stems of tiny wine glasses. A compound in red wine has been shown to improve health and survival in mice fed a high-calorie diet. Treatment with resveratrol, a plant-derived molecule found in red wine, prevented many of the health consequences of obesity, even as mice gained weight.

David Sinclair, an HMS associate professor of pathology who led the research, first identified resveratrol in a screen of molecules that enhance the activity of Sirt1, the mammalian version of the protein Sir2 that has been shown to affect life spans in yeast and other lower organisms. Since then, resveratrol has been demonstrated to increase life span in worms, fruit flies, and fish. This study, published online in *Nature* on November 1, is the first in a series of studies by Sinclair's group to determine whether resveratrol has the same impact on mammals.

PHOTO: ALLOY PHOTOGRAPHY/VEER

Living Lean

So far, the most reliable way to extend the life span of an organism is through caloric restriction. Since Sir2 seems to mediate the effects of caloric restriction in some lower organisms, Sinclair's team has been investigating whether manipulating the equivalent pathway in mammals can achieve the same benefits without cutting back on food. Joseph Baur, a postdoctoral fellow in Sinclair's lab and first author on the paper, says that studying the compound's effects in high-fat diets also makes sense given the prevalence of overweight and its known health risks. "Obesity," he says, "tends to accelerate a lot of aging-related diseases."

The study compared three groups of mice: one fed a normal diet; another that began a high-calorie, high-fat diet at middle age; and a group that began the same high-calorie diet but were simultaneously treated with resveratrol. After six months of treatment, mice that received resveratrol had a significantly higher survival rate. At 114 weeks of age, 42 percent of treated mice had died, compared with 58 percent of their untreated peers fed a high-calorie diet.

Resveratrol did not prevent mice from gaining weight on a richer diet, but it did prevent obesity-related health problems. Untreated mice who followed the high-calorie diet had swollen livers filled with fat deposits. The livers of the treated mice, however, looked normal. Mice in the group treated with resveratrol had healthier hearts, comparable to those of normal mice; lower levels of blood glucose and insulin; and higher insulin sensitivity. In a test of motor skills, the resveratrol-treated mice outperformed untreated overweight peers and even showed improvement with age.

The team also examined gene expression changes in the liver tissue of the mice. They identified 153 pathways that were significantly changed by either the high-calorie diet alone or the high-calorie diet plus resveratrol. In 144 of them, resveratrol produced an effect opposite that of a high-calorie diet; in other words, says Baur, "If a pathway went up in comparison to a standard diet, resveratrol made it go down"—and vice versa.

Missing Pieces

One of the study's surprises is that resveratrol seems to have uncoupled the health consequences of being overweight from the fat itself. "By looking at the physiology of these mice, you would think they are lean healthy mice, but they're fat healthy mice," Sinclair says. The implication, he adds, is that "fat isn't necessarily bad if you can block its effects."

Matt Kaeberlein, assistant professor of pathology at the University of Washington, says the study suggests that taking resveratrol or a similar compound could be beneficial for people who are obese or consume a high-fat diet—which unfortunately includes most people in the United States and other developed countries. But the study leaves open many questions, such as how resveratrol works and whether it can mimic the effects of calorie restriction in lean animals, which Sinclair's laboratory is currently testing.

The attempt to translate the pathways controlling life span in lower organisms into mammals has generated a great deal of debate. "Because the biology is so complicated, many of these pathways tie together," says Kaeberlein. "It's difficult to untangle."

Sinclair believes that the compound is keeping mice healthy by triggering the same life-extending response that a strict diet does. He notes, however, that, "There's a lot to figure out about how resveratrol works." His team used a proxy measure of Sirt1 activity to show that the enzyme was more active in mice treated with resveratrol. Sinclair doesn't rule out the possible involvement of other pathways, and the team is currently testing Sirt1's role by treating Sirt1–knockout mice.

Sinclair believes that because resveratrol is produced when plants are stressed, it may be one of many plant compounds that can trigger a "survival response" in animals that consume them. "It could be that we've evolved to sense molecules from the plant world," he says, adding that certain components of plants are not just beneficial as antioxidants or anti-inflammatories but are actually sending signals that change physiology.

Glasses should not yet be raised in toast to these findings, however. The daily dose of resveratrol given to mice in this study is the equivalent in humans of 100 glasses of wine, so its role at normal dietary levels is unknown.

Rafael de Cabo, the study's co-senior author and an investigator at the National Institute on Aging's Laboratory of Experimental Gerontology, hopes this study will spur new methods for testing the effects of aging in the body. Using longevity as an endpoint is onerous because studies on mammals can take years or, in the case of primates, decades.

"We need to find out what the exact targets are that resveratrol is hitting within fat tissue and organs," de Cabo says, as well as understand how caloric restriction affects the entire body of an animal. Only then can scientists start to unravel the puzzle of how these interventions extend life. ■

Courtney Humphries is a science writer for Focus.

ON RED ALERT

Researchers at Brigham and Women's Hospital (BWH) have faund that eating mare red meat may be assaciated with a higher risk far harmane receptor–positive breast cancers in premenapausal wamen. This research appears in the November 13 issue af the *Archives of Internal Medicine*.

"This study suggests that dietary factars may be related ta a waman's chance af develaping this type af breast cancer, a disease that is an the rise in American wamen," says lead authar, Eunyaung Cha, a researcher at BWH.

Harmone receptar–pasitive breast cancers are characterized by tumars in which grawth is stimulated by the levels of estragen (ER+) ar progesterane (PR+) circulating in the bady. Previaus studies that have examined the assaciatian between breast cancer and red meat assessed diet in midlife or later, did nat distinguish by hormane receptar status, and are largely incanclusive.

In this study, researchers evaluated the associatian between breast cancer and red meat cansumption in 90,659 female nurses aged 26 ta 46 who are part af the Nurses' Health Study II. The researchers fallawed the participants fram 1991 thraugh 2003 and gathered data on red meat cansumptian and breast cancer develapment.

Out af this group, which excluded postmenopausal women and thase wha had previausly had cancer, researchers identified 1,021 wamen wha had develaped breast cancer. Amang those with information an harmane-receptar status, 512 cases were ER+/PR+.

The researchers split the wamen into five graups based an haw much red meat they ate and faund that thase with the highest intake af red meat, mare than one-and-a-half servings per day, had nearly dauble the risk far harmane receptar–positive cancer campared with thase with the lawest intake af red meat, which was fewer than three servings per week.

Researchers suggest several bialagical factars that may be related to the association between red meat and ER+/PR+ breast cancer, including carcinagens faund in caaked ar processed red meat, hormone treatments of cattle far grawth purpases, and the type af iran faund in red meat.

"The reason the amount af red meat consumed by a premenapausal waman was related ta her breast cancer risk is unknawn," says Cho, who is also an assistant prafessor of medicine at Harvard Medical Schaal. "But this study shaws that the assaciatian is strang and that mare research shauld be dane to further explore this connection." ■

Scientists and physicians recall the defining moments

that have ignited their innovations in medicine.

Sparks of inspiration

EVEN IF WE COULD ASSEMBLE A TIMELINE of innovations made at Harvard Medical School—and by its graduates everywhere—during the past two-and-a-quarter centuries, we could never portray the minds and hearts behind those discoveries. We could never recapture the moments of inspiration, the years of dedication, the decades of determination. We asked just a handful of Harvard Medical School graduates and faculty members to recall their own sparks of inspiration, whether from the puzzle of an infant dying of stroke or an insight stemming from the unexpected warmth of tumors. What we found in their stories was defiance, an unwillingness to be constrained by conventional wisdom. In refusing to accept the tenets of their time, they have proved that it's indeed the thought that counts.

PHOTO: JOSEPH DEVENNEY/THE IMAGE BANK/GETTY IMAGES

Ernest Darkoh defies the skeptics and helps a nation save itself.

Eye of the storm

by ANN MARIE MENTING

BOTSWANA HAD LARGELY ESCAPED the HIV epidemic that rampaged through Africa during the 1980s. A peaceful republic with immense diamond wealth, the nation had prospered since its independence in 1966, achieving high rates of literacy and immunization and life expectancies that averaged 68 years. The nation's idyllic days were shattered in the early 1990s, however, when HIV invaded. Soon, Botswana's achievements were in tatters.

By 2000, nearly 39 percent of the country's adults were infected with HIV. With families in mourning, children orphaned, and the country's core working population dying on average before the age of 40, Botswana was, according

NAME: ERNEST DARKOH

TENET CHALLENGED:
HIV treatments in Africa are impossible because of costs, logistics, and the stigma associated with AIDS.

SPARK OF INSPIRATION:
The limitations of health care delivery systems in Africa—which contributed to the early death of a friend—outraged him and fueled his sense of mission.

PHOTO ANDY NELSON/CHRISTIAN SCIENCE MONITOR

to its president, Festus Mogae, being "threatened with extinction."

It was into this crisis that Ernest Darkoh '98 stepped when he arrived in Botswana in 2001. Part of a team charged with assessing the country's chances of mitigating its AIDS epidemic by providing free antiretrovirals to all in need, the assignment was, for him, a perfect match.

Darkoh was born in the United States of Ghanaian academics. As a child, he moved to East Africa with his parents, who held professorships in Tanzania, and, later, Kenya. The toll that crime, poverty, and rickety health care systems took on the people of those nations troubled the young Darkoh. Inefficiency touched everyone; his own parents often had to wait for paychecks caught in bureaucratic tangles. So did sorrow; when Darkoh was 19, a friend died because local hospitals refused him treatment, fearing he had AIDS. "His death," says Darkoh, "ignited a sense of outrage in me."

Darkoh returned to the United States for his college education. After earning degrees in chemistry, biochemistry, and molecular biology at the University of Wisconsin and medical and public

PHOTO: PETER VAN AGTMAEL/POLARIS IMAGES

health degrees at Harvard, he pursued a master's degree in business administration from Oxford. The blend satisfied his desire to enhance his health care training with solid business principles so as to better meet the demands of the developing world. It also provided him the agility he would need to confront the devastation of AIDS to an African nation—and to counter skeptics who viewed his work as a hopeless endeavor.

Dawn's Early Light

Botswana's president wanted to answer the epidemic's assault quickly and decisively. At this same time, representatives from the drug giant Merck and its corporate foundation and from the Bill & Melinda Gates Foundation were looking for a country with which they could join forces and implement a comprehensive program that would fight the spread of HIV. The three groups formed a partnership with the government of Botswana and ACHAP, the African Comprehensive HIV/AIDS Partnerships, was born. This new group provided the impetus the African nation was seeking.

To Darkoh, this collaboration represented, "a fortunate coincidence of purposes and intent." ACHAP arranged for Darkoh and the team, all from the management-consulting firm McKinsey & Company, to join with Botswana's Ministry of Health in determining what it would take to establish a national antiretroviral program.

The McKinsey team found that more than one-third of the approximately 300,000 HIV-infected people in Botswana needed antiretroviral therapy immediately. The team also devised strategies for ramping up the nation's infrastructure and for identifying areas in which capacity and capability needed to be strengthened or developed, including communication and education programs, training programs for health care providers, and a system for tracking and monitoring patients, laboratory samples, and medication use.

Botswana's national treatment program was launched in January 2002, and the program, called Masa—meaning "new dawn" in Setswana—was established. Impressed by Darkoh's work, ACHAP and Botswana's Ministry of Health asked him to head up Masa. He jumped at the opportunity—and into a job with monumental demands.

"It was uncharted territory," says Darkoh. "In epidemiological terms, a disease that affects 1 percent of a population is a catastrophe. With almost 40 percent of its adult population infected with HIV, Botswana faced a cataclysmic situation. As much as anything, we needed to bring hope to people who felt hopeless."

Within 15 months, the program had enrolled 6,000 patients at four treatment

It is heartening to see the change in attitude. People understand that regardless of their HIV status, they have viable options that allow them to live full lives."

centers; more than 3,000 patients visited one clinic alone to receive antiretroviral therapy. A year later, the program had quadrupled the number of patients receiving antiretroviral therapy and had increased the number of clinics to an even dozen. Botswana was soon reaching 16 percent of its people who needed antiretrovirals, the greatest outreach achieved at that time by an African country. By November 2004, the program had 34,000 patients on antiretrovirals, a figure that represented 9 percent of all people receiving such therapy worldwide. Botswana is now providing treatment to more than 70 percent of those in need.

The pace set in the program's first two years left Darkoh little time to rest. He juggled the logistics of setting up new clinics and laboratories, developing a nationwide tracking system for patients, and ensuring a steady supply of trained care providers in cities, towns, and villages. And he put out fires sparked by the sheer heat of the program's progress.

"It was a sprint every day," says Darkoh. "Although the program's roll-out was phased, we had to move fast. We couldn't allow the early clinic sites to become overwhelmed with demand, and we had to ensure that people everywhere could get to a clinic easily, without traveling long distances. So once we knew the teething problems that pilot sites faced, we made adjustments to minimize those problems and quickly set up new sites."

"I also kept pushing to get more people tested," Darkoh says. "I knew it was imperative that we started treating people before they became very sick. The only way to do that was to determine who was eligible for antiretroviral therapy."

"We also hoped to make a different type of citizen," adds Darkoh, "to empower people by providing them the information they needed to make behavioral choices. Why should a billboard promoting condom use interest you when you don't know your HIV status? We needed to make it personal."

Darkoh's wish became a reality when Botswana changed to an "opt-out" testing system. Previously, the country had followed the practice used in most places: Patients visiting a clinic would be counseled on HIV and then given the choice of being tested for the virus. Such "opt-in" approaches usually yielded few takers. In making the check for HIV part of the standard laboratory battery of tests patients received at clinics, Botswana did more than just increase the number of people who were tested for HIV—it also defused some of the stigma associated with the test, a crucial aspect for members of such a tightly knit population.

Having people learn their HIV status helped expand the pool of individuals eligible for antiretroviral therapy—and lengthen the queues at Masa's clinics. Aside from adding to wait times, long queues meant that less critical patients often had to step aside to allow those with severe symptoms to receive attention. Too many steps out of line meant fewer opportunities to have therapy monitored, a prescription that, over time, only added to the ranks of those who were severely ill.

To solve this dilemma, Darkoh split the lines, and, analogous to checkouts in groceries, established queues for patients with fewer needs and queues for patients with many needs. By identifying days and times for clinic visits by specific patient populations, this strategy increased the number of patients seen in any one clinic, and, more important, allowed patients who were not desperately ill to be monitored regularly.

Global Operations

The Masa program continues to add to the numbers of people being tested and treated. And with more than 30 sites up and running, the program has established treatment centers at every referral, district, and primary hospital in the country. Adherence to treatment regimens has proven to be solid, as evidenced by self-reports, attendance at scheduled appointments, and measures of viral suppression among patients. Best of all, the nation's mood has shifted from despair to hope.

"It is heartening to see the change in attitude," says Darkoh. "People understand that regardless of their HIV status, they have viable options that allow them to continue to seek—and live—full lives."

The program's success has also caused skeptics—who had believed any attempt to deliver HIV treatments to people in Africa were doomed from the start—to fall silent. Those fighting the epidemic in other African nations are now telephoning Darkoh to ask how the Masa program could work in their country. Although he is no longer in charge of the program, having helped transfer it to local management, Darkoh welcomes the calls. In fact, he recently joined with two colleagues to form BroadReach Healthcare, a company that designs health care delivery and treatment programs that can quickly be scaled up from concept to country-sized.

Although satisfied with his accomplishments in Botswana, Darkoh is clearly aiming for a time when the model he honed in that country multiplies into multinational, multi-disease programs that operate with the efficiency of the best business practices and the sustainability of a long-lived organism. Until then, one country at a time, he's perfecting his scalability model, ensuring it is nimble and fit, capable of meeting the demands any epidemic may throw at it. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.

NAME: JOAN BRUGGE

CHALLENGE TACKLED:
Learning how a cell becomes concerous requires an understonding of the intricate pothways and mechonisms thot govern its behovior.

SPARK OF INSPIRATION:
She crofted on innovative model of breast epithelial cells that con be used to decipher how genes and their proteins drive the concer process, providing clues thot moy one day help exploin a disease thot took her sister's life.

Joan Brugge chips away at the secrets of a disease that claimed her sister.

Signal corps

by ANN MARIE MENTING

GIVE JOAN BRUGGE A problem to solve and she's good to go. It's a skill she developed early. Passionate about mathematics, she formulated her career plans while still in high school: a degree in the field followed by a career educating future generations to the beauty and satisfaction found in unraveling problems and knitting their solutions.

Then life presented Brugge with an unsolvable problem, one not of formulas but of family. Her sister Mary Pat was diagnosed with a brain tumor. Brugge, accustomed to teasing forth answers to tough questions, found herself confronted with impenetrable ones: what had caused the tumor, and how could her sister's life be saved? But aside from a stray comment from her sister's neurosurgeon that one day viruses would likely be found to play a significant role in carcinogenesis, her inquiries were met by silence.

With a clarity sharpened by grief over her sister's death, Brugge recast her future. Solving problems would still be central to it, but now those problems would be microscopic, not mathematic. Brugge revamped her college studies, adopting biology as her major and taking on an independent study of viruses and oncogenesis. A summer laboratory internship introduced her to research, and she was captivated: "The small project I was responsible for introduced me to the scientific process and gave me a sense of the thrill that scientists experience when they explore uncharted paths. I became consumed by the need to do research."

For more than 30 years, Brugge has been busy charting some of those paths through her investigations of genes and proteins, especially of the ways in which their activities contribute to cellular behavior, both healthy and aberrant.

Sniffing Out the Truth

Since stepping into the world of scientific discovery, Brugge has never been tempted to look back. She has often taken great delight, however, in looking sideways.

PHOTOS FOR THIS STORY KATHLEEN DOOHER

"My colleagues and I were like bloodhounds following the scent, hoping to be led to where the protein was produced and where it was expressed."

"I followed one protein for most of my early career," says Brugge. "It was a long search to understand its function in normal cells and then to understand how permutations of that function could cause a normal cell to turn cancerous. The search took me in totally unexpected directions, ones far afield from cancer. But each detour gave me insights into the nature of the pathways that the protein controlled."

The protein that Brugge tracked—pp60$^{v\text{-}src}$—is one produced by both the cellular and viral forms of the *src* gene. Brugge had isolated the protein while working as a postdoctoral fellow in the laboratory of Ray Erikson at the University of Colorado in the late 1970s. Their discovery of what is now called v-Src rocked the field of cell biology; they had found what many held to be the holy grail of oncogenesis.

The isolated protein turned out to be an enzyme that transferred molecular groups called phosphates from a cell's energy source to other proteins. Scientists learned that such phosphorylations regulate how a cell proliferates, becomes invasive, and even survives. In her own laboratory, Brugge began to zero in on how the protein regulated normal cellular processes.

"My colleagues and I were like bloodhounds following the scent, hoping to be led to where the protein was produced and where it was expressed," says Brugge. "Our studies pushed us to investigate neurobiology, platelet biology, cellular adhesion, and intracellular signaling pathways."

Her peripatetic investigations were also pushing Brugge to consider new research opportunities. In 1992, she left academia to become the scientific director of ARIAD Pharmaceuticals, a Cambridge, Massachusetts–based biotechnology start-up. There Brugge planned to expand her investigations of the signaling pathways that dictate the disease process and to begin investigations of how cells respond to signals from proteins in their environment, a process known as signal transduction.

For five years, Brugge conducted her research while juggling the administrative and travel demands of the fledgling company. Although the research thrilled her, she was dogged by the knowledge that her laboratory time was too curtailed to allow her to do investigations that met her own high standards. In addition, Brugge was again pondering a new line of inquiry, one that would, she hoped, produce an in-vitro model that closely replicated how cells organize themselves in living tissue. So, in 1997, with a track record of stellar research in hand and innovative investigations in mind, Brugge accepted a professorship in the Department of Cell Biology at HMS; in 2004, she became the department's chair.

A Bad Influence

In the field of oncogenesis, researchers have largely relied on fibroblasts to study cancer development within the laboratory confines of a Petri dish. The reasons are practical; connective tissue cells are easy to culture and to render immortal, thus allowing scientists to monitor changes in cellular development and function through umpteen generations.

Most human tumors, however, originate in epithelial tissue. So instead of clinging to the established paradigm, Brugge fashioned an in-vitro model using breast epithelial cells. She knew epithelial cells behave quite differently when allowed to organize into structures that resemble those they form in living tissue. When so organized, these cells function as they do in the body. Salivary cells, for example, will produce saliva, and breast cells will produce milk. Growing epithelial cells in Petri dishes was unnatural; the rigid surfaces could not mimic the elastic structures of the body.

Brugge's model drew upon pioneering work using extracellular matrix proteins. First, she filled pea-sized chambers with a gel enriched with such proteins as collagen and laminin. Then she suspended breast epithelial cells in the gel. Her model worked beautifully. The cells organized into three-dimensional structures that resembled the milk glands of human breast tissue—cellular spheres whose hollow centers are kept clear by a surveillance system that gives any infiltrating cell a greeting so brutal that the wayward cell initiates the death process known as apoptosis.

With a viable model developed, Brugge could now better track the pathways and mechanisms that change normal breast cells into cells that proliferate excessively, migrate into tissue that is not their turf, and become so robust that they can fend off the body's messages to cease and desist. In short, Brugge wanted to reconstruct the disease process one gene at a time.

"We set up a series of experiments to identify the genes involved in breast cancer and to try to fit those genes into known pathways regulated by growth factors and adhesion receptors," Brugge says. "Our screens using HER2 showed us the power of this model."

The HER2 gene is found in the genomes of breast cancer cells, particularly those forming a noninvasive type of cancer called ductal carcinoma in situ. In cells with this gene, DNA duplication often goes awry: It gets caught in a loop, repeatedly duplicating the sections of the chromosome that contain HER2. Such duplication can increase the cell's HER2 presence by 25- to 30-fold, an amplification that brings with it an overproduction of the protein produced by the gene and, consequently, a barrage of the signal that protein is responsible for giving the cell. Unregulated growth results, and a

tumor forms. "It's like hitting the gas pedal," says Brugge. "Cellular replication goes out of control."

Although it is possible to target HER2 therapeutically, the cells can become drug resistant. Brugge thought a stronger approach might be to home in on the pathways and mechanisms by which the gene and its protein acted. This would, she reasoned, provide a more universal understanding of the cancer process as it would highlight the cellular missteps central to the formation of any type of tumor.

Brugge and her research team introduced HER2 into the model system and waited. The results were eye openers: The cells not only proliferated madly, but the structures they formed had cells in the normally empty interiors of the spheres. Signals from HER2 proteins, therefore, exercised a double whammy; they caused hyperproliferation and they turned off the structure's sentinel system, allowing the proliferating cells to live when they should have died. In addition, the group found that when cells with amplified HER2 also contained a certain growth factor, they became capable of metastasizing.

"It was striking," says Brugge, "how closely the architecture of the cultured structures resembled the architectures of the different types of tumors found in vivo."

The model system could replicate the disease process—at least as undertaken by one cancer-related gene. Brugge was now ready to define the roles of other genes implicated in breast cancer.

Check It Out

This year, Brugge, together with Joshua LaBaer, director of Harvard's Institute of Proteomics, established the Breast Cancer 1000 initiative—the first public library of proteins that are reliably expressed in breast cancer. Containing 1,300 complementary DNA, stable forms of the molecule that are capable of producing the sought-after proteins, the library will allow researchers to interpret the choreography of cancer. Is, for example, a particular protein that is altered in a breast tumor cell a principal player in the disease process or a victim of it? How does a protein contribute to the diseased cell's ability to invade, grow, or change how it relates to its environment?

To evaluate the range and functionality of the library, Brugge and her team inserted into the model system nearly 300 complementary DNA whose roles in the disease process were already known. Each was then subjected to a series of screens that identified how the DNA's protein product contributed to the disease process. Their screens not only validated the system as a testing mechanism but also uncovered some genes not yet known to play a part in the disease's biology.

With studies of proteins and the cancer process well under way, Brugge has begun looking at what happens higher up the cellular ladder, at the genomic level and, ultimately, at a systems, or whole body, level. It is unlikely her search for answers will diminish or her list of questions shorten. The college student who looked to others to make sense of her sister's illness now knows that, through her own research, she can cut windows into the darkest of black boxes.

"I'm enjoying the research I'm now doing more than any science I've done," Brugge says. "I'm addicted to discovery, to being presented with an unanswered question, pulling together the information needed to build a hypothesis, designing an experiment to test that hypothesis, and then interpreting the results. It's what drives me—the exploration of the unknown." ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.

The thin red line

by PAT MCCAFFREY

Judah Folkman devotes decades to proving an unpopular theory.

JUDAH FOLKMAN '57 GOT HIS FIRST LOOK AT cancer in its natural habitat when he was removing tumors from patients in the late 1950s. Folkman is now the Julia Dyckman Andrus Professor of Pediatric Surgery at Harvard Medical School, but back then he was a surgical resident at Massachusetts General Hospital.

The malignancies he routinely encountered in the operating room bore little resemblance to the neat slices of tissue he'd studied mounted on microscope slides, or the flat bed of cells growing in Petri dishes in the research laboratory. Actual tumors, he realized, were a bloody mess.

During an operation, Folkman could feel the heat—like that of a child's fever—from a large mass. He saw hundreds of blood vessels, some coming from great distances to supply the malignancy. Indeed, he spent hours in the operating room carefully cauterizing each small bleeder before finally removing the tumor, all in an effort to prevent dangerous blood loss.

After his residency, Folkman was drafted and assigned to the Naval Medical Research Institute in Bethesda for two years. There he implanted cancer cells into isolated rabbit and dog thyroid glands. Tiny tumors appeared, but then stopped expanding at a size smaller than the diameter of a pencil point. Yet when he transplanted these tiny white tumors into mice, the tumors rapidly grew to the size of a marble and reddened. What, he wondered, was the difference?

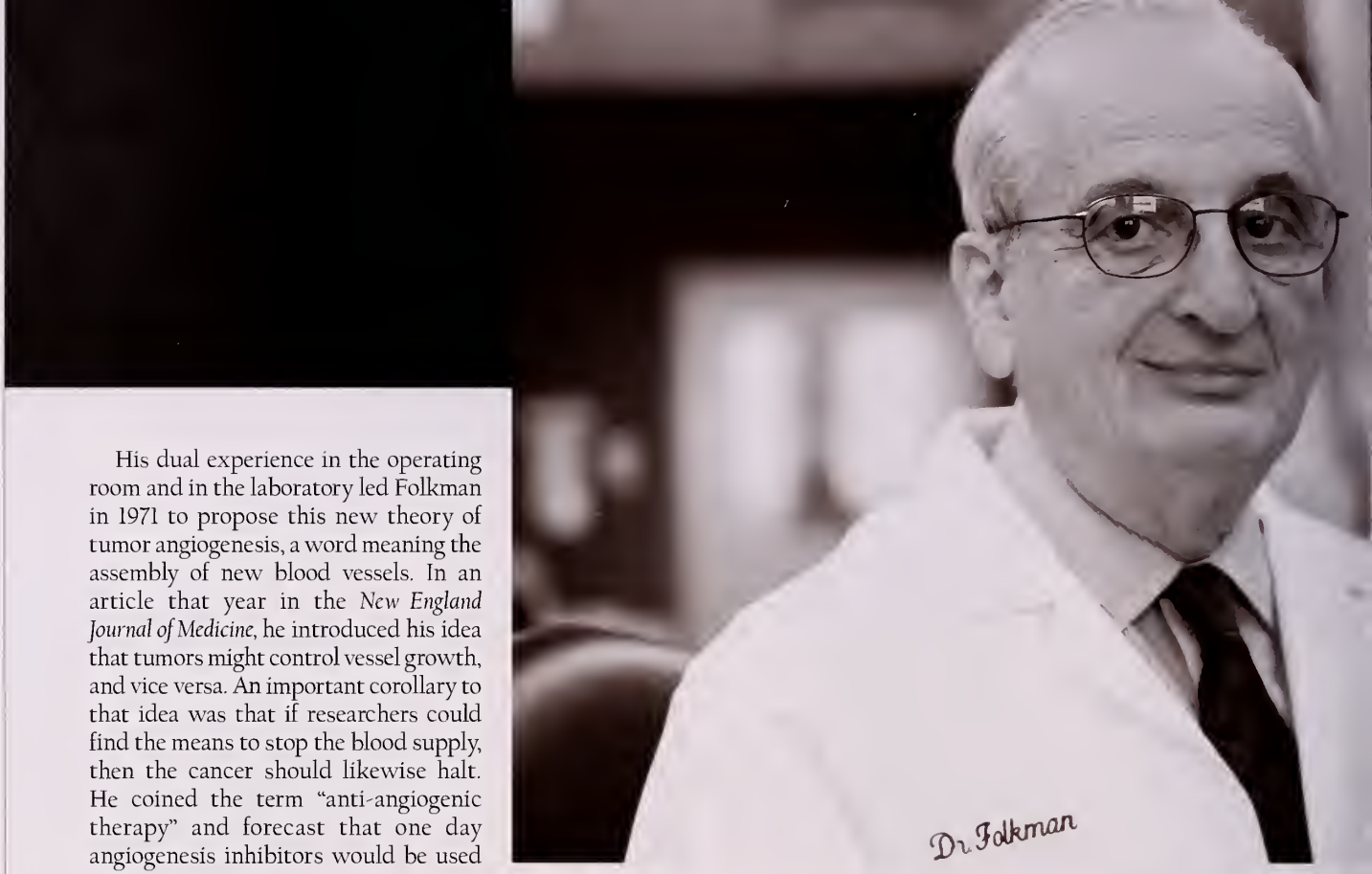
It turned out the answer had been right in front of him, on the operating table. Tumors, he realized, were like any other tissue in the body. They needed a robust blood supply to grow and thrive. Without that, they might stay small and sometimes even disappear. What if, Folkman thought, the secret of these large tumors' success depended on their forming their own new blood supply? What if the cancer cells produced factors that drove the production of blood vessels and the blood vessels fed the tumor?

PHOTOS FOR THIS STORY KATHLEEN DOOHER

NAME: JUDAH FOLKMAN

NEW TENET OFFERED:
Tumors spur the development of their own blood vessels, a process called angiogenesis.

SPARK OF INSPIRATION:
The warmth of tumors made him wonder whether they, like the other tissues in the body, needed their own blood supply—and whether they could be starved if that blood supply was cut off.



His dual experience in the operating room and in the laboratory led Folkman in 1971 to propose this new theory of tumor angiogenesis, a word meaning the assembly of new blood vessels. In an article that year in the *New England Journal of Medicine*, he introduced his idea that tumors might control vessel growth, and vice versa. An important corollary to that idea was that if researchers could find the means to stop the blood supply, then the cancer should likewise halt. He coined the term "anti-angiogenic therapy" and forecast that one day angiogenesis inhibitors would be used to treat cancer.

All of this turned out to be true—although it took three decades to prove it. His 1971 article, which at first gained little notice, is now viewed as the seminal publication in a large and growing field of research. On the clinical side, eight different angiogenesis inhibitors are now on the market to treat a variety of cancers. At least 30 more are in human trials, aiming for Food and Drug Administration approval.

Moreover, cancer is not the only disease in which the use of angiogenesis inhibitors has made a difference. These blood vessel blockers are the newest and most effective treatment ever for age-related macular degeneration, the leading cause of blindness in people over 65. The condition causes sight loss when blood vessels infiltrate the retina, cloud it, and eventually destroy it. In a recent clinical trial, treatment with an angiogenesis inhibitor stopped the disease in 95 percent of patients. Amazingly, it restored vision in four out of ten treated, to the point at which legally blind people regained enough eyesight to drive a car.

A recent editorial in the normally understated *New England Journal of Medicine*, coming 35 years after Folkman's original proposition, called the treatment "miraculous."

Doubt Yields to Data

Ironically, the surgeon's skill contributed to the early and persistent doubts among other researchers that cancers could grow their own blood supply. That's because a properly excised tumor looks entirely different from how it first appeared to the doctor. With the vessels painstakingly sealed off, the previously engorged tissue is drained of blood, its vessels collapsed. The idea that tumors could be magnets for blood vessel growth didn't jibe with the cold, white lump that the pathologists found deposited in their sample pans outside the operating room door.

"People thought I was crazy," Folkman says. "And some pathologists were very critical. But they didn't see what I saw in the operating room. Back then, no one—including my colleagues at Harvard—believed that tumors needed new vessels. They thought cancers would get along fine on the existing vessels. That red color, they said, was inflammation from dying tumor cells. They didn't believe tumors made a specific protein to regulate vessel growth. Anyway, they said, they knew of no molecules that could make blood vessels grow."

All of the objections to the idea of angiogenesis were beliefs, Folkman says, and when scientists hold to beliefs, it takes data to change their minds. Those data began to accrue a few years later, when Folkman and his postdoctoral fellow Robert Langer, now a professor at HMS and MIT, demonstrated that a protein purified from tumor cells could coax blood vessels to grow. The assay they developed, which has since become the gold standard for measuring tumor angiogenesis, involved placing a few tumor cells in a pocket of a rabbit's eye tissue. The cells would sit, growing slowly, until after a few weeks blood vessels would begin to snake out over the eye, heading for the tumor. Once the blood supply reached the cancer cells, tumor growth exploded. Simply by looking at the eye, Folkman and Langer could tell that the tumor was producing an angiogenic factor, which they set out to isolate.

In one key experiment, the researchers replaced the tumor with the protein factor extracted from cancer cells. To do this, they had to invent a way to package the protein in a sustained-release depot. Langer did that, and to the researchers' delight the blood vessels read the depot as a tumor and began to grow toward it.

More exciting than that, says Folkman, was what happened when they let the blood supply develop and then removed the depot. Within a few weeks, the blood vessels disappeared.

"Back then no one—including my colleagues at Harvard—believed that tumors needed new vessels. They thought cancers would get along fine on the existing vessels."

"That was a big moment," Folkman remembers. "When we saw that the constant presence of the protein factor was needed to maintain those vessels, we knew our idea was right. We knew that, in theory, an angiogenesis inhibitor could work to cut off the blood supply to tumors. From then on, it didn't matter what the critics said. I knew they were wrong."

The next decade brought ups and downs in the laboratory. In 1994, another postdoctoral fellow identified the first angiogenesis inhibitor made by cells themselves, a protein the researchers dubbed "angiostatin." When the laboratory showed that a relative of angiostatin, called endostatin, prevented tumor metastasis in mice, the race was on to launch the recombinant protein into clinical trials for cancer. In those trials it appeared that endostatin had failed, because even though tumors and their metastases remained stable with arrested growth for up to three and a half years in some patients—and the patients remained active and without side effects—the tumors did not regress and so were graded as "no response."

Other kinds of inhibitors quickly replaced endostatin. Many of the current anti-angiogenic drugs are antibodies and small molecules that mimic, at least in part, endostatin action. Recently a new version of endostatin proved effective and is now in use in China, a development Folkman hopes will be replicated in the United States.

The Next Big Thing?

Today, the Folkman domain encompasses 80 researchers in 15 affiliated laboratories on the top two floors of the Karp Family Research Laboratories of Children's Hospital Boston. Around one conference room, framed enlargements of the covers of research journals chronicle the fits and starts of their progress. When his ideas were less popular, Folkman hung up the first covers featuring their work to encourage his researchers to plod on. Now, the walls are blanketed with more than 30 reproductions, each documenting one eureka moment after another.

In the conference room one floor above hang the many prizes Folkman has received for his work. Arrayed on the walls are dozens of plaques and framed certificates from organizations, governments, and universities all over the world. Folkman proudly points out one of the latest—the Helen Keller Prize for Vision Research, in honor of his group's work on new treatments for macular degeneration.

At 73, Folkman still has the surgeon in him. He roams the lab in a clean white coat with his name stitched in red letters over the breast pocket. Underneath he wears a pressed shirt and necktie. He has passed the age at which many researchers retire, but that is a move he is not contemplating.

"When Verdi was in his seventies," Folkman says, "people asked him what his best opera was, and he answered, 'I haven't written it yet.' When he was close to eighty, he wrote *Falstaff*. For me, the ideas keep coming, and maybe because of experience, they're better and better. As long as these kinds of ideas are coming and we're working on them, I should keep on going." Those words might seem boastful, but Folkman's soft voice lends them a more modest tone.

His latest project is finding ways to treat cancer before it becomes a surgeon's problem. Recent work has revealed that we all carry microscopic tumors throughout our bodies, but only one tumor in a thousand turns into a cancer that is diagnosed and requires treatment. Folkman showed that all the others stay small because they are not angiogenic. Once the tumors switch on blood vessel growth, though, the cancer grows rapidly, and symptoms appear. If a doctor could tell by a blood test that the angiogenic switch has flipped, Folkman theorizes that the patient could then be treated immediately with anti-angiogenic medicine, and the tumor would wither.

Folkman makes an analogy to the treatment of infections before antibiotics. "There were no drugs for infections, only surgeons. If you had an abscess, the surgeon would find it and drain it. Now, we rarely need to do that. If we have a patient with an infection, we don't do a CAT scan or an MRI to localize it. We just look at the blood count and treat."

He'd like to do the same for recurrent cancer. "If we had a really good biomarker—a sentinel protein in the blood, for example—we could conceivably use the biomarker as a guide in our treatment of recurrent cancer or for diagnosing a nascent cancer before it manifests symptoms. Such indicators could also help us design more effective treatments by detecting a tumor before it is anatomically visible or by showing us that a patient's anticancer drugs have lost their punch.

"Now I know today that few people believe that. They say you can't treat a tumor you can't see, or you can't treat a patient who has no symptoms."

Yet Folkman and his colleagues are trying this very approach for the first time with a patient at risk for recurrence of tumors. "If and when we get our results," Folkman says, "we'll publish them. It may be a unique case of treating cancer guided only by a biomarker in the blood, without actually seeing the recurrent tumor."

"And no one will believe it," he says with a laugh. "But after the hundredth patient, they may. And after that, my guess is that such treatment could become a common occurrence." ■

Pat McCaffrey is a freelance writer based in Auburndale, Massachusetts.

Jim Yong Kim advocates for change in the moral debate over treatment.

The possible dream

by ANN MARIE MENTING

BRINGING HEALTH CARE TO THE poor living in the farthest corners of countries, in urban angles and alleys, and in the difficult spots in between is not only feasible, it's the only fair thing to do, insists Jim Yong Kim '91. ■ Kim is an idealist, an advocate who, whether working among the poor in resource-scarce countries or among the powerful in the halls of the world's leading health organization, has but one goal: health care for all.

"When I was at Harvard, I heard an old aphorism that students entering medical school are among the most idealistic of all students," says Kim, "but they're among the least idealistic by the time they leave."

Kim's career has given lie to that adage. Throughout medical school, he held onto his global care ideal so firmly that he capped his degree with a doctorate in medical anthropology. "I wanted to figure out how could I push forward a process that would provide health care to everyone," says Kim. "That question has stayed with me."

To listen to Kim, it is easy to hear the strength of his passion for health care equality and to discern the skill he has shown in channeling that passion into programs to dispel care disparities. It does not take much to realize this unabashed idealist has been quietly composing a health care policy revolution.

Field Day

Kim started putting his ideals into practice while still a student at HMS. In 1987, he connected with Paul Farmer '90, another HMS student–idealist consumed by the same goal. Kim joined Farmer in the newly launched Partners In Health (PIH), a Cambridge, Massachusetts–based nonprofit dedicated to supporting health care programs for the poor in Haiti, especially those living with HIV. Together the young physicians built the organization, and, in 1994, at the urging of Father Jack Roussen, a long-time PIH supporter, expanded it to include treatment programs for people living

NAME: JIM YONG KIM

CHALLENGE TACKLED:
People in developing countries were dying of multidrug-resistant tuberculosis—and the complex treatments that could save them seemed out of reach.

SPARK OF INSPIRATION:
He convinced generics manufacturers to make off-patent drugs available at a fraction of their original cost.

PHOTOS FOR THIS STORY KATHLEEN DOOHER

with tuberculosis in Carabayllo, a shantytown on the fringes of Lima, Peru.

In Peru, Kim and Farmer were decried as *médicos aventureros*—medical adventurers—by some and dismissed as Harvard "egghead" researchers by others, but were lauded as health care advocates by most. The situation they faced in Carabayllo would demand the fearlessness implied by those monikers.

At that time, tuberculosis was rampant among Peru's poor. The standard treatment for the disease was failing a significant number of patients; officials in the health ministry accused the patients of neglecting to take all their medications. The consequences of inadequate compliance are grim: Such an environment would allow the tuberculosis bacterium to develop resistance to the drugs used in standard therapy. And then Roussen fell ill.

The PIH team flew the priest to Boston for treatment, where they found out—too late—that the bacteria causing Roussen's illness were resistant to every first-line tuberculosis drug. The priest's death not only saddened Kim, it dismayed him as well: Roussen had not been treated for tuberculosis before he fell ill, so an improper use of medications could not have contributed to his resistance.

Kim realized that drug-resistant forms of tuberculosis were thriving among Peru's poor; first-line medications were no longer effective. For people who were contracting multidrug-resistant tuberculosis (MDR-TB), standard therapy, even when well followed, would always fail. New therapies were needed.

Providing treatments for MDR-TB would be expensive, but Kim and Farmer were convinced it was possible to develop and implement complex interventions that could treat the MDR-TB epidemic sweeping through Peru's poor. The trick, as they saw it, would be convincing others.

"We needed to shift the moral debate," says Kim. "We saw the MDR-TB scourge as the way to do this. It's a communicable disease, and we're all living in one world. It was a disease that actually scared wealthy people. So we kept pushing and kept getting press. Soon we had the ear of people who could help move forward our program to treat MDR-TB."

PIH established community-based treatment programs to assist people with MDR-TB in Haiti and Peru and, later, in Russia. Building on the DOTS (Directly Observed Treatment Short-course) plan for treating tuberculosis, which had been embraced by the World Health Organization (WHO), Kim and Farmer devised a DOTS-Plus program that used both first- and second-line drugs to treat MDR-TB. One obstacle—getting the needed drugs cheaply—immediately loomed. But Kim, who had analyzed the Korean pharmaceutical industry while researching his dissertation, realized this was a problem that could be solved relatively easily.

Kim knew that as a drug migrates from branded-compound status to that of off-patent generic, its sticker price nosedives, ultimately falling by as much as 95 percent. Kim succeeded in getting generics manufacturers to produce the needed drugs, which had been off patent for some time, and to sell them at 1 to 5 percent of their open-market cost. Kim's trailblazing effort paid off for PIH—and others. More than 30 countries have since followed Kim's plan and acquired top-line drugs at bargain-basement prices.

The PIH MDR-TB program achieved an 85 percent cure rate in its first group

Although the program did not reach its goal of bringing treatment to three million people, it did succeed in getting treatment to nearly one million, a previously undreamed-of achievement.

of patients in Peru, a rate that surpassed those of some of the best U.S. hospitals. The team's efforts among populations in Haiti and Russia also succeeded, as did a similarly structured HIV-treatment program PIH launched in Haiti.

World Premiere

To the PIH team, accumulating evidence of the feasibility and efficacy of their community-based treatment programs meant they could move to what they considered the next stage—changing international health care policy governing infectious diseases. To do this, they needed to persuade policymakers to push for treatment programs for a troika of killers: malaria, tuberculosis, and HIV.

The PIH team decided to open a second front. Farmer would stay in the field, continuing to establish the merits of novel treatment programs in resource-scarce settings, while Kim would take on the challenge of working for change in international health care policy. It was a daunting task, but one Kim was set to tackle.

In 2004 Kim stepped onto the global stage, taking a sabbatical from his position as codirector of the HMS Program in Infectious Disease and Social Change and moving to a post as director of the WHO's HIV/AIDS department. He arrived at the Geneva-based organization during its transition from one director general to another. It was in this environment of change that Kim set about agitating the institution's leaders to think on a scale large enough to take on the tasks demanded by global epidemics.

"When I went to the WHO, I told the director general I wanted to do something revolutionary in HIV treatment," says Kim. "His predecessor had floated an idea for bringing HIV treatment to 3 million people by 2005 and I told him that I thought this was an initiative we should undertake. It would be a difficult target—perhaps even impossible—but I thought it was something we should embrace.

"He asked whether we could make the target, and I said, 'I think we can. But it's more important that we take a stand and insist that we try.' He gave me the okay and we went for it. Boy, did we get attacked."

To make what became known as the 3 by 5 Initiative a global mandate, Kim helped marshal support from the 192 member nations of WHO's World Health Assembly and worked to get the endorsement of other groups that made up UNAIDS, the United Nations umbrella organization that oversees its HIV/AIDS programs. Kim was seeking resolve on the part of these global institutions, a plan that would set targets and make demands of countries, something with teeth in it, rather than what he considered the organization's usual action—a polite declaration of commitment with little incentive for implementation.

The entire UNAIDS family acted, supporting not only the effort to push nations to deliver antiretrovirals to half the people who needed help within two years' time but also to assess each country's progress every six months. Kim soon found that people either loved or hated the idea; there were few shades of gray.

"The donors were extremely unhappy because we hadn't asked whether they would pay for such an effort. Health ministers in some nations hated it. They were angry because I would point to numbers to show which countries were failing to move on the plan.

"But others celebrated the initiative—poor people, people with HIV/AIDS, and people who worked to help those without access to treatment. And the Canadians loved it—and gave us 80 million dollars, bless them."

Although the program did not reach its goal of bringing treatment to three million people, it did succeed in getting treatment to nearly one million, a previously undreamed-of achievement. Overall, the 3 by 5 Initiative has been deemed a success, credited with raising the bar on global public health initiatives, pushing organizations and countries to think big, act big, and fund big programs designed to fight diseases threatening to kill or incapacitate millions of people and hobble the progress of dozens of nations.

In late 2005, Kim returned to Harvard, where he has since taken leadership roles as chair of the HMS Department of Social Medicine and as director of the Harvard School of Public Health's François-Xavier Bagnoud Center for Health and Human Rights.

"First-year medical students have told me they want to learn how to build successful intervention programs to a scale that makes them effective for entire countries," says Kim. "We're trying to respond. I'd like Harvard Medical School to teach the science of implementation for health care programs not only in the developing world but also in this country."

To this end, Kim is helping to develop coursework that melds entrepreneurial ideas and good business practices with the idealistic aims of providing health care to the world's poor. The effort, he says, will produce a program in global health effectiveness in which medical students can learn to build treatment programs that are infused with the fruits of medical research and clinical innovation: They will be taught the science of global health care implementation.

By crafting a tool that can be used in the implementation of programs that will provide health care to all, Kim is doing more than just remaining true to his goals. He is swelling the chorus working for social justice, populating it with young physicians eager to put their ideals into practice. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.

Carla Shatz rewrites some of science's most sacred scriptures.

Second sight

by PAT MCCAFFREY

IF YOU ASK NEUROBIOLOGIST CARLA Shatz to replay the highlights of her career to date, this is what she won't mention: In 1976, she became the first woman to receive a doctorate in neurobiology from Harvard. She was one of the first two female junior faculty members hired in basic science at Stanford University School of Medicine, and the first woman to receive tenure there. In 2000, Shatz became head of the neurobiology department at Harvard Medical School, the first woman in the history of the department to be its chair and only the second woman in the history of the School to chair a basic science department.

Shatz never expected to become a pioneer or a role model for women scientists, and those accomplishments aren't her real highlights, she would say. For her, the memorable moments have all happened away from the limelight. Above all else, Shatz says, she is a scientist. And for that reason, the most exciting moments of her career have invariably come in the laboratory. What's more, she'll tell you, each was all the more memorable for being completely unexpected.

"One of the most enjoyable and engrossing parts of life as a scientist is that the work resembles a big mystery story," Shatz says. "With each twist and turn you get surprises."

Seeing Is Believing

Shatz, the Nathan Marsh Pusey Professor of Neurobiology at HMS, has made her mark in her chosen field with studies of how the eye and the brain get properly connected during early life. She was the first to see waves of electrical activity carried by nerve cells undulate across the retina during fetal development, as the eye tested and retested its connections to the visual processing regions in the brain. In effect, she says, she caught the neurons rehearsing for vision before birth—long before the eye ever sees the light of day.

NAME: CARLA SHATZ

TENET CHALLENGED:
The brain operates in isolation from the immune system, o state called immune privilege.

SPARK OF INSPIRATION:
Having documented some of the surprises the broin still holds for scientists, she persevered when skeptics dismissed her findings that an immune system molecule helped regulate the ability of neurons to rewire.

PHOTOGRAPH FOR THIS STORY: KATHLEEN DOOHER

As she went on to demonstrate, the coordinated, in-utero communication between the nerve cells in the eye and the visual centers of the brain organizes and strengthens the connections between neurons. The rehearsal stage simply prepares the cells for becoming hardwired into visual circuits, which happens later in response to light.

When Shatz made that discovery, she and her students were watching the activity of neurons in a cat retina under the microscope. They were not surprised to see the neurons firing away—they expected that—but they were astonished to find entire groups of neurons signaling in a coordinated pattern.

"That was incredible," Shatz says. "Everyone who saw it just said, *Wow.* The waves of activity were completely unexpected, and we couldn't believe how beautiful they were. I still play the movie we made then, because so many people can't believe it. And we didn't either, at first."

What Shatz saw turned out to be a leap in our understanding of how communication between groups of cells can organize whole brain circuits. "Cells that fire together, wire together," she says.

"What's really neat is since we discovered those waves, researchers have found them all over the brain during development," Shatz says. "Spontaneous nerve activity was known to exist, but the discovery that neighboring neurons are all correlated and firing together turns out to be crucial for understanding the way connections get set up, remodeled, and rewired."

Immune to Criticism

The next big surprise came when Shatz decided to look for the proteins controlling the wiring process in the fetal brain. To do that, she and her laboratory team analyzed patterns of gene expression in the brain tissue of cats and mice

"That Was Incredible. Everyone who saw it just said, *Wow.* The waves of activity were completely unexpected, and we couldn't believe how beautiful they were."

during normal development as well as when nerve signaling in the visual system had been blocked with a toxin.

The gene that fell into their net was a stunner. As with the neuronal waves, it was at first hard to believe. What showed up in the remodeling neurons was a protein belonging to the major histocompatibility complex (MHC) class I family of molecules, the cell-surface proteins that help the immune system recognize foreign substances. Proteins produced by the cell's MHC gene cluster are best known for their role in the rejection of transplanted tissue. Cells all over the body use MHC proteins—but they had never been found in the nervous system before.

The researchers wrote up the results, but their paper was rejected immediately. In a note sent back with their manuscript, an editor scoffed at the work, writing that "everyone knew" neurons don't express MHC class I molecules.

"The editor suggested we must have made a major mistake," Shatz recalls. "Now, at that point we could have said, 'Okay, we made a mistake,' and just moved on. But it was a very robust result, and because I'd had other surprises from the brain, I realized that we should pay attention to this."

"It turns out we'd run smack into a real dogma of biology," Shatz says with a smile. At that time, everyone believed that the brain operated in isolation from the immune system, a state called immune privilege. Shatz believes that other researchers had also run into the MHC protein in the brain but had set their observations aside in deference to the prevailing view. The more experiments Shatz and her colleagues conducted, though, the more evidence emerged that MHC proteins were not only present in the brain but were also critical to brain wiring in fetal and early life.

Once again, Shatz's work held implications far beyond the visual system. In adults, the ability to rearrange neuronal connections is necessary for learning and making new memories, and she found that mice genetically engineered to lack MHC proteins displayed a profound defect in their ability to rewire in response to new experiences.

"We realized these molecules aren't just in the visual regions of the brain, and that they are important not only in fetal life, but also through adulthood," Shatz says. "That was a critical step forward. At that point, several other researchers approached me and confessed, 'Well, I didn't believe it until you showed it.'"

In the immune system, MHC molecules help cells recognize each other by linking with partner molecules called receptors found on cell surfaces. Together, MHC and its partner receptor act like a lock and a key to bring cells together for communication. The researchers thought that MHC might act in the same way in the brain, by helping to bring nerve cells together at their synapses—the special connections between two nerve cells. After a five-year search, Shatz recently found a partner for MHC in the brain.

The work has generated a great deal of excitement, Shatz says, and already scientists are telling her informally that they've linked the MHC protein and its partner to diseases. "I think we're looking at the tip of the iceberg. This may prove to be our biggest advance in the lab."

Everybody Freeze

As important as synaptic changes are for development and learning, at some point the rewiring has to stop—too much synaptic flexibility can be just as bad as too little. Most of the molecules identified in the past 20 years have been positive regulators of this remodeling. The experiment that Shatz and coworkers conducted with MHC's receptor showed that these molecules act in the opposite way—they put the brakes on synaptic plasticity rather than act as an accelerator.

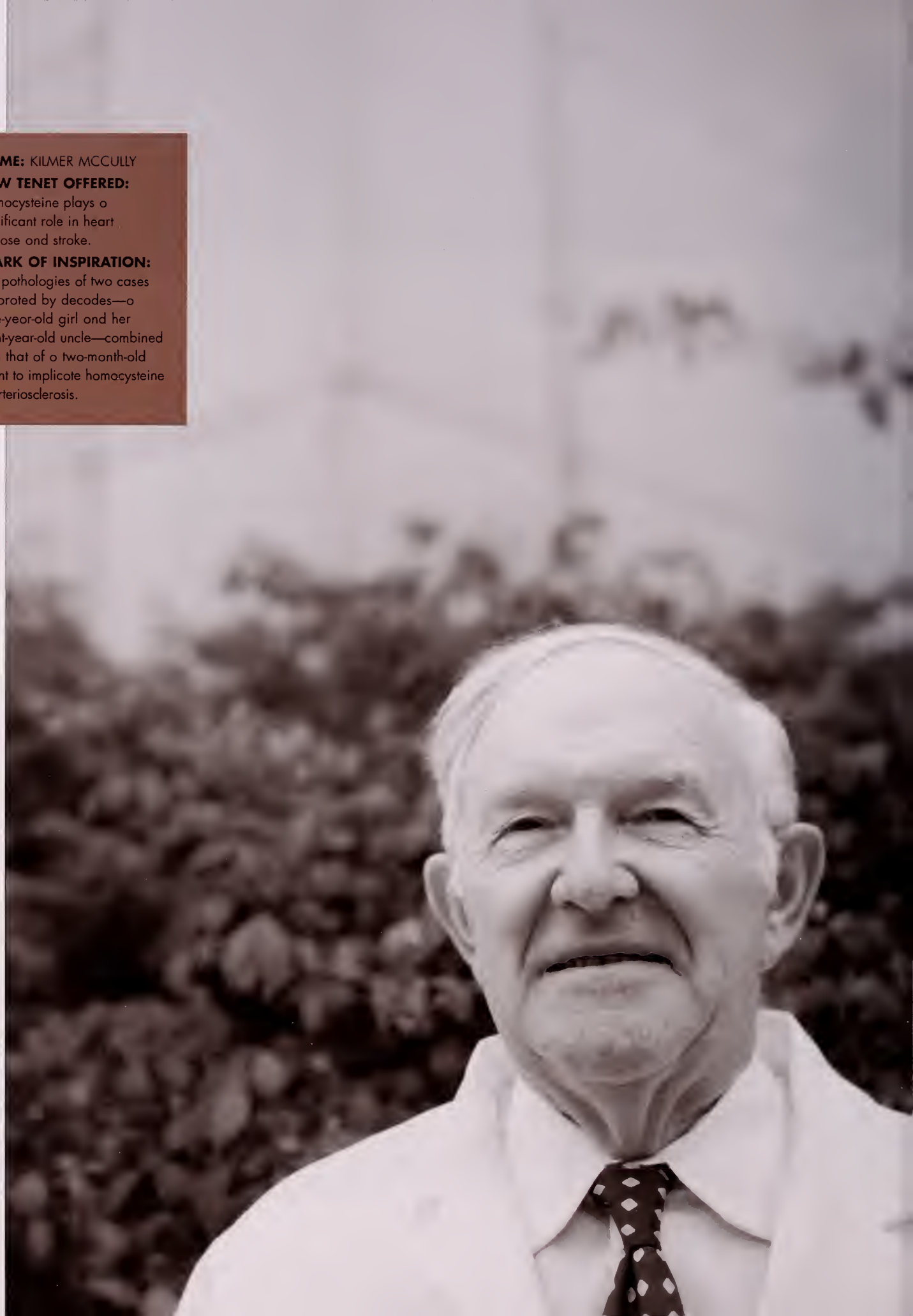
That observation has therapeutic value, Shatz says. "If you could block the signaling between MHC and its partner receptor in adults after stroke or brain damage, you might be able to regain the incredible plasticity that's present in fetal life and childhood. That may let you develop a pill to block this pathway and enhance memory—maybe something that would even help in Alzheimer's disease. Or perhaps it would allow you to re-create circuits or to get one circuit to take over the functions of a damaged one."

This latest insight brings Shatz full circle to her high school days and the reason she decided to pursue neurobiology research in the first place. At that time, her grandmother, a vibrant, active woman, suffered a debilitating stroke, and Shatz was frustrated that doctors could do nothing to help.

Later, when Shatz decided to attend graduate school, two uncles, both neurologists, called her to tell her she was making a big mistake; she should be heading to medical school instead. Recognizing that neurologists at the time had terrific diagnostic tools but few treatments to offer, she told them, "I'm going to go into the lab and get to work and see if maybe one day I can help people by making discoveries."

But even having said that, Shatz admits that the link between her work and a possible treatment for brain injury is the most unexpected result she's had so far. "To think that, after all those years ago, when I told my uncles I was going to do research, I would be sitting here saying, 'Look, I've found a protein in the brain that might lead to drugs for stroke'—that's just amazing." ■

Pat McCaffrey is a freelance writer based in Auburndale, Massachusetts.



NAME: KILMER MCCULLY

NEW TENET OFFERED:
Homocysteine plays o significant role in heart diseose ond stroke.

SPARK OF INSPIRATION:
The pothologies of two cases seporoted by decodes—o nine-yeor-old girl ond her eight-year-old uncle—combined with that of o two-month-old infant to implicote homocysteine in arteriosclerosis.

PHOTOS FOR THIS STORY: KATHLEEN DOOHER

Collateral damage

Kilmer McCully connects the dots in cases separated by decades.

by ANN MARIE MENTING

A THIRTY-YEAR OLD protocol, six pathology slides, and one small, misshapen lump of tissue-studded paraffin were treasures to Kilmer McCully '59 when he scavenged them from pathology jetsam that had been stored in the attic above the old Massachusetts General Hospital morgue.

It was 1968 and McCully, fresh from a residency in pathology, was on a mission to review information on a case he had heard described during morning rounds.

Those rounds, led by the newly appointed chief of human genetics, John Littlefield '47, had touched on the case of a nine-year-old girl who had been seen at the hospital. The young girl's symptoms included flushed cheeks, dislocated lenses, and mild mental retardation. The diagnosis was homocystinuria, a metabolic disorder caused by the defective activity of an enzyme.

The diagnosis alone was enough to tweak the young pathologist's attention. Homocystinuria had been characterized just four years earlier. But what really registered on McCully's mental radar was a statement by the pediatrician in charge of the case: In 1933, the child's uncle had been diagnosed with similar symptoms and, at age eight, had died of stroke.

Curious as to whether a link existed between the metabolic disorder and the death-dealing stroke, McCully had begun his hunt through the crammed glass, wax, and paper archives of the hospital's pathology department. With his finds in hand, he studied the protocol, re-embedded the tissue, prepared new slides, and reviewed the pathology of the young stroke victim. And, just as the pathology report stated, the child had had arteriosclerosis of the carotid arteries with thrombosis and stroke. How interesting, thought McCully.

Four months later, however, when a genetics rounds report included information on a two-month-old baby boy who had died of pneumonia and brain damage, interesting became fascinating. This child, who had been admitted because of failure to thrive, had been diagnosed with cobalamin C disease, a form of homocystinuria caused by a defect of the enzyme methionine synthase. When the amino acid methionine, produced during protein metabolism, breaks down in the body, homocysteine is produced. If methionine's metabolism is disrupted, as in cobalamin C disease, the levels of homocysteine build up in the plasma.

The homocysteine disorder that had afflicted the nine-year-old girl, and—by

Exploring associations that have previously escaped notice are intellectual currency. What he was to learn was that intuiting and measuring such links could also cripple a career.

genetic extension—the eight-year-old stroke victim, resulted from a mistake in the enzyme cystathionine β-synthase. McCully reasoned that if the infant's pathology also showed arterial plaques, high homocysteine levels would be the common attribute of, and perhaps the unknown culprit in, the vascular damage that contributed to their deaths.

McCully headed for the hospital's pathology department. He re-examined the infant's tissues and found clear evidence of rapidly progressing arteriosclerosis.

For McCully, as for other physicians and researchers, exploring associations that have previously escaped notice are professional and intellectual currency, clues that can save lives or change scientific tenets. What McCully was to learn was that intuiting such links—and having the curiosity to measure their validity empirically—could also cripple a career.

Strings Too Short to Use

The implications of the children's pathologies grabbed McCully wholesale. Before finishing his pathology fellowship at the hospital, McCully had spent years in research, including a stint studying cholesterol in the laboratory of Konrad Bloch, the biochemist who won a Nobel Prize for his work on the biosynthesis of that steroid. Yet McCully had never heard of an association between the amino acid homocysteine and stroke or heart disease.

"I've always been interested in new ideas and how they fit together," says McCully. "What I do is locate the different threads and try to find their pattern."

Memories of classes at HMS surfaced, and he scoured his freshman-year notes for jottings from a nutrition lecture in which Fredrick Stare had discussed studies showing that methonine supplements reduced cholesterol levels and arterial deposits in monkeys fed high-cholesterol diets. Vague recollections of a connection between vitamin B_6 and homocysteine had McCully knocking on the door of genetics chief Littlefield. Their conversations spurred him to look through other medical school notes, this time for references to studies linking vitamin B_6 deficiency with arteriosclerosis in monkeys. These concepts started to weave together in McCully's head; he began to write the first paper on what would become his homocysteine theory of arteriosclerosis.

"I had trouble sleeping," McCully recalls. "My wife told me I was spouting chemical formulas in the middle of the night. It was an intense period."

McCully proceeded methodically, remaining true to his years of research training in the laboratories of such notables as Paul Zamecnik '36, James Watson, and, of course, Bloch.

McCully was a solitary worker but took soundings of his findings periodically by discussing them with colleagues. With the help of Benjamin Castleman, the chief of the hospital's pathology department, McCully obtained slides of authenticated cases of homocystinuria from laboratories at Johns Hopkins and in Northern Ireland and compared them with his slides. The pathologies matched. He submitted the tissues of the two-month-old boy to an electron microscopist for his interpretation of the pathology: His reading jibed with McCully's. And more biochemistry chats with Littlefield helped solidify McCully's translation of just what homocysteine could be doing at the molecular level. Through these contacts, McCully checked and validated his findings.

Publish and Perish

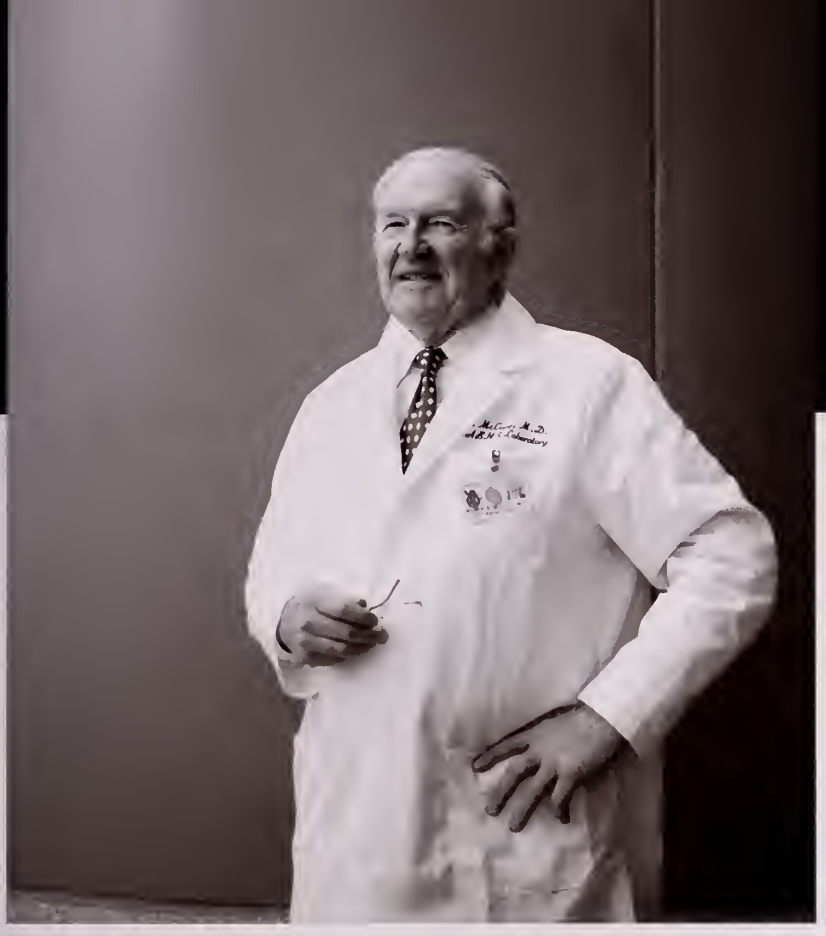
One early spring day in 1969, McCully left the hospital and headed for the nearest post office. He gripped an envelope containing his manuscript describing the vascular pathology of homocysteinemia and its implications for arteriosclerosis. "I didn't want it to get lost in the house mail," he says. "So I walked it over." Three weeks later an editor at the *American Journal of Pathology* contacted him. His manuscript had been accepted without change and was to be published immediately. In the ensuing months, McCully was flooded with reprint requests.

"Scientists all over the world understood what I was saying and thought this concept was new and important." McCully pauses and his voice lowers as he remembers the significance those responses held for him as a young scientist. "I was astonished. It was extremely gratifying."

The paper's publication began a furious stretch of research for McCully. He set up shop in a first-floor laboratory in the hospital. There he studied cell cultures of children with homocystinuria, discovered a sulfate metabolism pathway for homocysteine, and induced homocysteinemia in rabbits, producing vascular lesions that matched those in children with disorders of homocysteine metabolism and those found in adults with arteriosclerosis.

His research excited him, his results fascinated him, and his publications laid out the evidence for his theory of homocysteine's role as an arterial terrorist, damaging vessel walls, triggering plaque formation, and ultimately causing arteriosclerosis. He refined his theory, realizing that although genetic, hormonal, and toxic factors such as cigarette smoking contributed to high levels of homocysteine, the single most important factor was the dietary imbalance between too much methionine from dietary protein and too low an intake of folic acid and vitamins B_6 and B_{12}—all needed to break down excess homocysteine.

His investigations even began to insert cholesterol into the equation—as a substance captured in the arterial



plaques formed in response to homocysteine-instigated damage, a secondary complication rather than the cause of the vascular changes. Funding rolled in, with the National Institutes of Health, the American Heart Association, and the American Cancer Society among the biggest sponsors.

McCully toiled at this level for seven years. Then everything turtled. In 1976, Castleman retired, and a new department head was appointed. From him, McCully learned that the climate had changed, that "the Harvard elders—he didn't specify who—just weren't interested in my research."

That same year, McCully's laboratory was moved out of the hospital's pathology department and for two years he was sidelined to a laboratory outside the department before being moved again, this time to a basement facility. His key technicians, research fellows, and students, fearing what they read in the academic tea leaves, began to depart. McCully needed to support his research with grants, but without the skilled assistants to help with that research, grant-gaining became impossible.

"In good conscience, I couldn't ask funders to support me under those conditions. So on January 1, 1979, I left. But I wasn't prepared for what would happen."

Divine Providence

For 27 months, McCully was unemployed—and seemingly unemployable. "I'd have interviews, but the same pattern would occur. I'd get some interest from an institute or hospital, I'd go for the interview, then all of a sudden everything would stop. One of my friends told me I was being blacklisted. I didn't know what to do. I wasn't sure why this was happening—or who was responsible."

A position became available at the Veterans Administration Hospital in Providence, Rhode Island, and McCully was invited for an interview—but soon a too-familiar chill began to cool the process. McCully was afraid. He was approaching a critical juncture. He had not worked for two years and had not kept up with continuing education requirements; his medical license was possibly in jeopardy. He needed this position.

So McCully sought the advice of William Homans, a respected civil rights attorney. For three hours, McCully told his tale to Homans. The attorney asked him to wait while he made some calls—Homans knew some members of Massachusetts General Hospital's Board of Trustees. A day later, the freeze seemed to break. McCully got the job, his license renewal was approved, and, in 1981, he began working in Providence.

McCully spent 20 years there, time that provided him the opportunity to continue his work on homocysteine; expand his general theory to identify the amino acid's role in aging, cancer, and arteriosclerosis; and explain his theory in more than 60 papers and two monographs, products of what remains for him a totemic process—empirical research.

Reflecting on those tough two years, McCully is still not sure why he was given the cold shoulder by the research community, although he speculates that his research had more than a little to do with it. That was, after all, the time when cholesterol was named as the most-wanted substance, the evildoer most in need of measure and control. Yet along came McCully, publishing papers showing that a high homocysteine level was the culprit behind arteriosclerosis and contending that homocysteine could be kept in check simply by changing the diet to include more fruits and vegetables, less protein, and vitamin B supplements.

McCully remains philosophical, however, realizing that what happened to him has happened to others who made discoveries out of step with their times. Now, as chief of the pathology department at the Veterans Affairs Medical Center in West Roxbury, Massachusetts, McCully continues his investigations. Other researchers are also pursuing studies in the area and finding links between high homocysteine levels and such debilitating conditions as cardiovascular disease and Alzheimer's disease, expanding a field that was once almost exclusively McCully's. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.

NAME: CATHERINE WILFERT

CHALLENGE TACKLED: Children were becoming infected with HIV through vertical transmission.

SPARK OF INSPIRATION: The successful use of AZT in treating HIV-infected adults could be duplicated in efforts to prevent mother-to-child transmission of the virus.

Catherine Wilfert turns her gaze to the smallest victims of HIV.

No child left behind

by ANN MARIE MENTING

THE KIBERA COMMUNITY SELF-HELP Programme in Nairobi, Kenya, provides children affected by AIDS with a haven. There they can learn carpentry and shoemaking, receive counseling on sex and HIV, and just be kids. The center also gives women widowed by AIDS or burdened with HIV shelter, care, and counsel. It was there, one day six years ago, that Catherine Wilfert '62 listened as nearly 40 beaming children serenaded her with chorus after chorus of "Happy Birthday to You."

"It was a truly unbelievable birthday," says Wilfert. "To be among those children reminded me that as overwhelming as the AIDS epidemic is, there is hope. I feel the work I am now doing is the most important of my life."

Many take the celebration of a birthday for granted, but for the children at the Kibera community program, growing older can be an accomplishment. Some, in fact, may be able to commemorate the passage of birthdays only because of research that Wilfert helped to conduct.

As scientific director of the Elizabeth Glaser Pediatric AIDS Foundation, Wilfert spends a good deal of time visiting sites where the foundation's efforts to stop the transmission of HIV from mothers to infants are under way. This work, however, is just the latest leg of a decades-long career during which Wilfert has studied how best to protect the smallest victims of the HIV/AIDS epidemic. Because of the research she and others have pioneered, tens of thousands of children in Africa—and throughout the world—are alive and healthy, beneficiaries of antiretroviral regimens devised not only to treat women infected with HIV, but also to protect their babies, born and about-to-be-born.

A Looming Shadow

When Wilfert arrived at Duke University in 1969, she was fresh from Children's Hospital Boston, where she had worked as a pediatrics resident and as

PHOTO: JOE FORNABAIO

"We didn't know how well children tolerated AZT. And we didn't know its risks for pregnant women. Yet we desperately needed answers on how to prevent HIV infection in babies."

an instructor and a fellow in the virology laboratory of John Enders. Her knowledge of how infectious microorganisms affect children made her a welcome addition to Duke's pediatrics group. Eleven years later, Wilfert had earned full professorships in pediatrics and microbiology and had been appointed chief of the medical center's pediatric infectious diseases unit. Although she had continued her investigations of such organisms as varicella, echovirus, and *Rickettsia*, she found her research—and interest—increasingly pulled in the direction of a newly discovered bully: HIV.

The epidemiological evidence made HIV a compelling subject. In North Carolina, as in other southern states, an uptick in the use of cocaine and injection drugs—and the risky behaviors often associated with their use—had migrated from metropolitan centers to rural communities. In the early 1980s, children constituted 2 percent of the recognized AIDS cases in the United States. By mid-decade, that percentage was rapidly changing, with annual projections for new HIV infections in children being tallied in the tens of thousands. That the projected numbers echoed those among women of childbearing age did not escape Wilfert's notice—or research lens.

By 1986, Wilfert had established herself as a leader in a new specialty—pediatric HIV/AIDS. That same year, she created Duke's pediatric HIV/AIDS program, one of the first of its kind in the nation.

From her studies of mothers and infants attending Duke's clinic and from the work of researchers in other clinics in the United States, Wilfert documented vertical transmission of HIV—the passage of the virus from mothers to infants during pregnancy, childbirth, or breastfeeding—as the chief cause of pediatric infection. To Wilfert, the devastation HIV was bringing to adults foretold a pediatrics disaster as well.

The Young and the Defenseless

AIDS manifests differently in children than it does in adults. Vertical transmission allows HIV an entrée to an immune system that is just learning to cope with environmental insults. Without much opposition, the aggressive virus disables the new immune system and renders the infant vulnerable to bacterial infections, including bouts with meningitis and pneumonia. Some infants also repeatedly contract chickenpox and other usually once-in-a-lifetime childhood diseases.

While adults infected with HIV—even those without access to antiretroviral therapies—can often live several years before showing AIDS symptoms, babies infected during gestation or through breastfeeding usually display symptoms within the first year of life. The virus kills 35 percent of its young victims by age one, 50 percent by age two, and 60 percent by age three.

From Wilfert's tracking of the pathogenesis and natural history of the virus among infants at Duke's clinic, she knew it was vital to find a treatment that could improve infants' chances of fighting the virus or block it from them in the first place.

A recently resurrected compound was about to fit Wilfert's bill. In 1985, researchers looking for drugs with anti-AIDS potential had dusted off a 20-year-old chemotherapeutic failure called azidothymidine (AZT). The scientists now found that AZT stalled HIV by increasing the number of immune cells in the body that fight the virus. Interestingly, AZT also proved to be an effective prophylaxis for adults who inadvertently exposed themselves to the virus through a needle stick or other contact with infected blood or fluids.

Wilfert thought AZT might be a viable pediatric prevention tool. The drug, however, had been tested only in adults. "Testing drugs in children always lags behind adult testing," says Wilfert, "so we didn't know how well children tolerated AZT. And we didn't know its risks for pregnant women. Yet we desperately needed answers on how to prevent and treat HIV infection in babies."

In 1989, she began researching the use of AZT for children infected with HIV and, when results showed promise, spread the word within the pediatric HIV/AIDS community. By 1994, the National Institute of Allergy and Infectious Diseases' Pediatric AIDS Clinical Trials Group, a group Wilfert chaired, conducted a large, multi-site study to test the safety and efficacy of AZT for HIV-infected pregnant women and their infants. The study, known as the Pediatric AIDS Clinical Trials Group protocol 076, or ACTG 076, produced groundbreaking results.

Vertical transmission was reduced by two-thirds among HIV-infected pregnant women who had taken AZT orally during the second or third trimester and intravenously during labor and delivery and whose babies had received AZT for the first six weeks after birth. Health providers finally had a means of preventing mother-to-child transmission of HIV.

Implementing the AZT protocol in the United States reduced infant infections from the virus more than 80 percent. The country's rates for vertical transmission plummeted from 25 percent to 2 percent; in 1999 North Carolina had only four reported cases of HIV transmission from mother to child. Wilfert had the tool she sought.

Yet as Wilfert looked at international transmission rates, she realized the

problem was far from solved. An opportunity to help stem the global rates of transmission presented itself in 1996 when she was recruited as the scientific director for the Pediatric AIDS Foundation.

"I was excited to take the job," says Wilfert, "because I would now be able to focus on international programs to prevent vertical transmission while being part of an organization with a long record of sponsoring research for HIV-infected children."

Baby Steps

Working in a nonprofit organization that funds programs in approximately 1,100 clinics in 18 countries means Wilfert's passport gets a workout. Although she has swapped the laboratory for the field, her contributions to research on effective ways to prevent mother-to-child transmission of HIV have not abated.

In Cameroon, South Africa, and other countries in sub-Saharan Africa, the foundation has been further evaluating antiretroviral regimens—including those involving the drug nevirapine—that offer women and babies prevention against HIV transmission. Although AZT remains a force in transmission prevention—and, together with nevirapine, is recommended for three months before childbirth—the delivery of this intervention presents problems for the health systems of many resource-scarce countries. Nevirapine, when administered in a single antepartum dose to the mother and a single dose to the newborn, has been shown to reduce vertical transmission 41 percent in breastfed babies for up to 18 months.

Worldwide, an estimated 530,000 children are infected with HIV each year—that's nearly one child each minute. With 90 percent of these infections linked to mother-to-child transmission, the stakes are high. Yet Wilfert continues to find promise in the incremental progress that characterizes the fight to halt vertical transmission of HIV. Noting that the pool of need remains great despite the foundation's outreach to more than two million pregnant woman in the program's half-dozen years, Wilfert admits, "That's a small number when you consider the 130 million babies born each year throughout the world—30 million in Africa alone. But it shows what can be done within the existing infrastructures of resource-scarce countries. These steps are incredibly important in our international effort to prevent mother-to-child transmission."

Wilfert's enthusiasm for her work is evident in her voice—strong and clear and laced with pragmatic optimism. With such hope, and continued research, her care-filled efforts may indeed help trump the deadly success of her viral opponent. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.

PHOTO: COURTESY OF THE DUKE UNIVERSITY HEALTH SYSTEM

by RAY BABINEAU

IT WAS A GLORIOUSLY SUNNY JULY DAY. I was in my sixty-third year, excited about moving into new office space, when I received a call from my internist. My recent PSA test, he told me, had shown a notable increase since the previous year. The absolute number was still low and likely insignificant, but he wanted to refer me to a urologist, just to be sure.

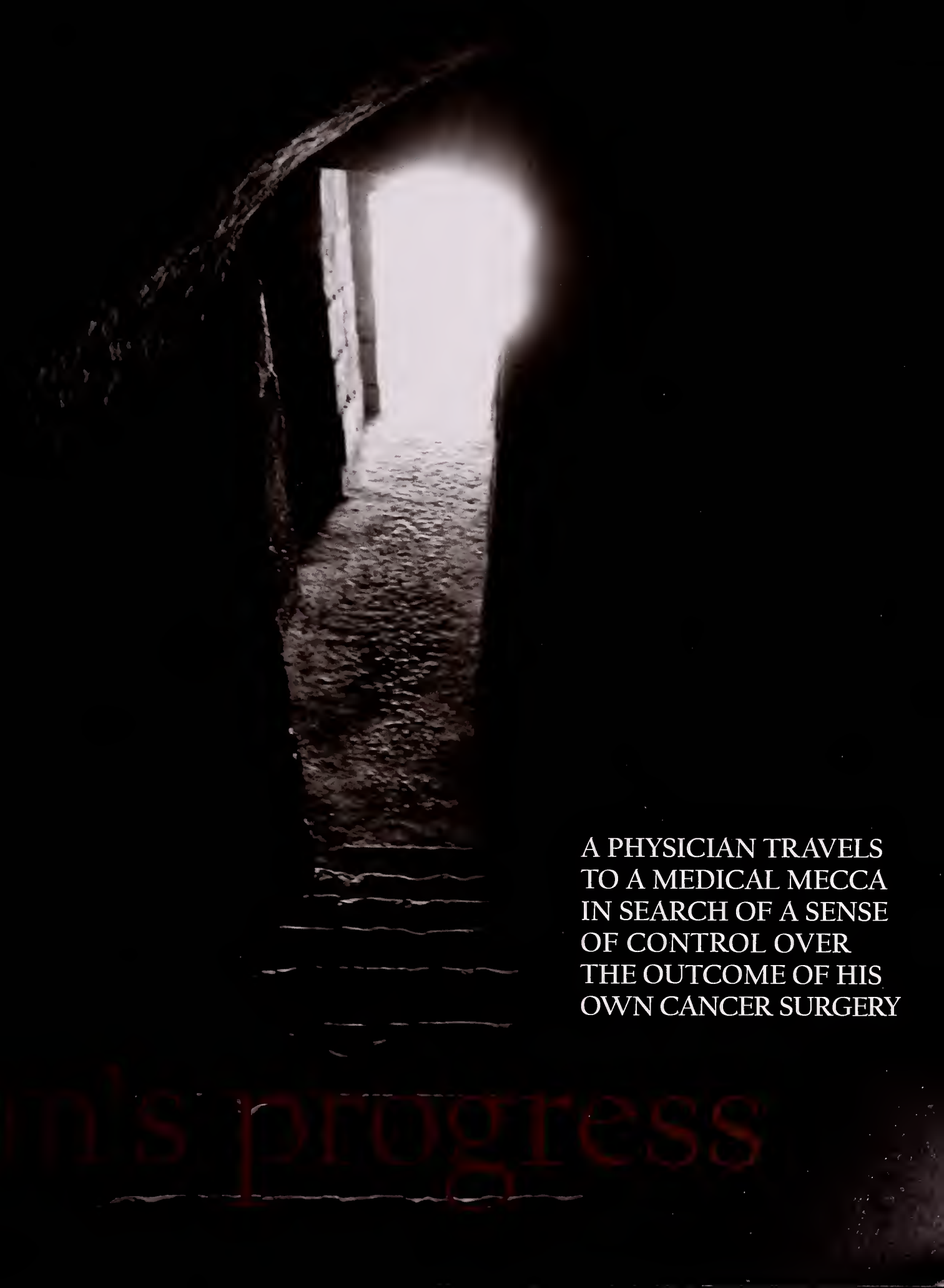
The remaining weeks of summer passed with consultations, antibiotics, repeat PSAs, and finally needle biopsies of my prostate. The biopsies were painless; the sharp jolt came several days later, on an equally sunny September day, when the urologist called. A community hospital had judged the biopsy slides to be suspicious but not definitive for cancer. The slides were being sent to the university-hospital pathologists for a second opinion. The sunshine of those two portentous days was a backhanded slap at my belief that I could detect auspicious patterns in nature.

I felt in perfect health, and my exercise and diet regimens were too rigorous to allow cancer. The names on the slides must have been switched, I thought, or perhaps a poor staining preparation had caused this questionable reading. Suddenly peevish, I wondered why the urologist, who was university affiliated, had used a community hospital for precious me? I held on to the thought that I simply could *not* have cancer, but as two weeks passed my conviction of health eroded. During repeated flights to the Internet I began gathering enough information about prostate cancer to fill several large three-ring binders. Soon I felt prepared to give a crash course in Prostate Cancer 101, and I understood well Samuel Johnson's aphorism: "When a man knows he is to be hanged in a fortnight, it concentrates his mind wonderfully."

On a follow-up visit the urologist told me that the biopsies did indeed show malignancy. I could consider a radical prostatectomy or radioactive seed implantation. The urologist favored the surgery, and he boasted of his ability to perform this complicated procedure in 90 minutes. He hurriedly disclosed the many possible complications and—I'm just sure—broke eye contact when he mentioned the risks of impotence and urinary incontinence as if they held equal weight with unevenness of closure at the wound. I knew all too well that those dreaded side effects of the conventional form of surgery he offered were frequent and could be powerfully life changing.

I seethed with a silent rage toward him, a rage I'd had difficulty directing at impersonal fate. I had read enough in the

PHOTO FREDERIC CIROU/VEER



A PHYSICIAN TRAVELS TO A MEDICAL MECCA IN SEARCH OF A SENSE OF CONTROL OVER THE OUTCOME OF HIS OWN CANCER SURGERY

n's progress

The Cleveland Clinic is one of the nation's medical meccas, set up for those who believe they must travel to find the medical care they seek. The trend is nothing new; human beings have always needed journeys to an Aesclepion, a Benares, or a Lourdes as a hope center, and these modern secular sites fulfill a similar need.

intervening two months to know that several of his statements were wrong or misleadingly oversimplified, and I felt contemptuous of his need to sell his own surgical services. When I asked about a specialized form of surgery that had a better chance of preserving potency, to my dismay he waved it off as experimental. My plan was then clear: flee that office with my x-rays and biopsy report in hand. I told him I needed time and might seek a second opinion. The atmosphere turned frosty. No sale.

The Wicket Gate

From my frantic Internet searches I had learned that the type of surgery I wanted—a nerve-sparing radical prostatectomy—had become well established since its development in the early 1980s. The procedure was now available in eight major medical centers in the United States, and I quickly settled on the Cleveland Clinic, both for its relative proximity to our home and because the name of one of its urological surgeons, Eric Klein, kept recurring in the literature.

Not only had Klein recently coauthored a book on prostate cancer, but he had also written the chapter on refinements to this meticulous surgical technique, which aims to preserve two precious nerves that take the long pelvic journey from spine to penis. This procedure takes about three hours to perform, not 90 minutes. I ordered the book sent overnight from the publisher, read Klein's chapter, and, given my unshakable reverence for the printed word, became convinced that Klein was the man and Cleveland was the place.

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Glossy brochures depicted the Cleveland Clinic as a large campus with an extensive scattering of buildings, each catering to a particular diagnostic or treatment function, and with several hotels catering to out-of-town patients and their families. My medical insurance covered out-of-town treatment, and making arrangements for the surgery proved easy. I found myself talking with Klein on the phone within days and, since I was convinced that surgery with him was the option for me—*sale*—I was scheduled for the operating table in four weeks. I felt relief at closure around one detail in a tide of uncertainty.

The Slough of Despond

Although she hid it bravely, this was a difficult time for my wife, Charmaine, as well. In our shared bed we turned on twin spits of worry. Sadly, I had to tell our two sons of my news and let them know they were at increased risk for prostate cancer. They promptly went out and got baseline PSAs to manage their own anxiety. I was seized with genetic guilt.

Those were tormented weeks with my patients as well. As their psychiatrist, I believed I should offer disclosure and time to discuss their reactions to the news. I ended up hearing more than I ever wanted to hear, hour after stressful hour. They recounted anesthesia deaths, fatalities on the operating table, complications, and infections. And they wondered—ever so delicately—about the risks of impotence, mirroring and elaborating my own worries.

The Cleveland Clinic recommended that I donate two units of blood in advance, which the local Red Cross would process and ship to the clinic for storage should I need autologous transfusions during surgery. It felt strange watching the blood flow from my body and knowing it would be encased in plastic, labeled, refrigerated, and consigned to the tender mercies of Federal Express and countless technicians along the journey to Cleveland. If all went without error, in a month we might be reunited miles from home, and my estranged blood could, if needed, resume its life-giving functions within me.

Klein's office had offered me a choice of dates, and the Friday workup day with surgery on the following Monday morning seemed best. I knew surgeons were usually at their best in the morning and early in the week, and I was trying to exert shreds of control—that comforting illusion—wherever I could. But we all fatigue. I hoped my presurgery weekend would not be the one during which my surgeon and his wife decided to divorce or learned that their teenagers were selling illicit drugs.

The Celestial City

The weeks passed. Charmaine and I arrived in Cleveland early on a Friday. Since the clinic was tailored to out-of-town travelers, we spent the entire workup day moving obediently from station to station for preoperative evaluation. It reminded me of having been processed into the U.S. Army, but with far more efficiency and courtesy. At the end of the day, I met Eric Klein. No, I had no more questions, but I *had* brought my copy of the book he had coauthored and wondered whether he would sign it for me. This *was* a first, he said, and, clearly tickled, autographed it, wishing me a complete recovery. I had obtained the book and its author. Could I be in safer hands?

As I was leaving his office, Klein joked that PSA would come to mean "Prostate-Specific Anxiety." I smiled but did not tell him that that meaning

had held true for years. How many men escape that concern?

Saturday and Sunday were unscheduled, so Charmaine and I had time to kill. We wandered around downtown Cleveland on a cheerless winter day, the weather finally cooperating with my patterns-of-nature theory. I feigned interest in museums and art galleries. We ate excellent meals and drank intemperate amounts of wine of a quality we had never dared buy before. We made love several times that weekend as if two or three decades of aging had been stripped away. Our passionate intensity was fueled by fears that Monday morning would bring dreadful possibilities: death on the operating table, news of inoperable cancer, or the surgical end to our ability to have intercourse. We absurdly tried once more on Sunday evening, failed miserably, laughed at ourselves, and collapsed into a troubled sleep. We had killed the weekend.

At four in the morning, the requested wake-up call came. With difficulty, I had persuaded Charmaine that it would be pointless for her to rise at that hour. She would have plenty of agonizing time that morning in various waiting rooms. As compliant as a sacrificial victim, I followed instructions for cleaning myself inside and out and descended to the hotel lobby. I checked at least twice with the desk clerk to make sure the shuttle bus was running at that early hour. He reassured me with a calm well practiced through countless encounters with fretful patients.

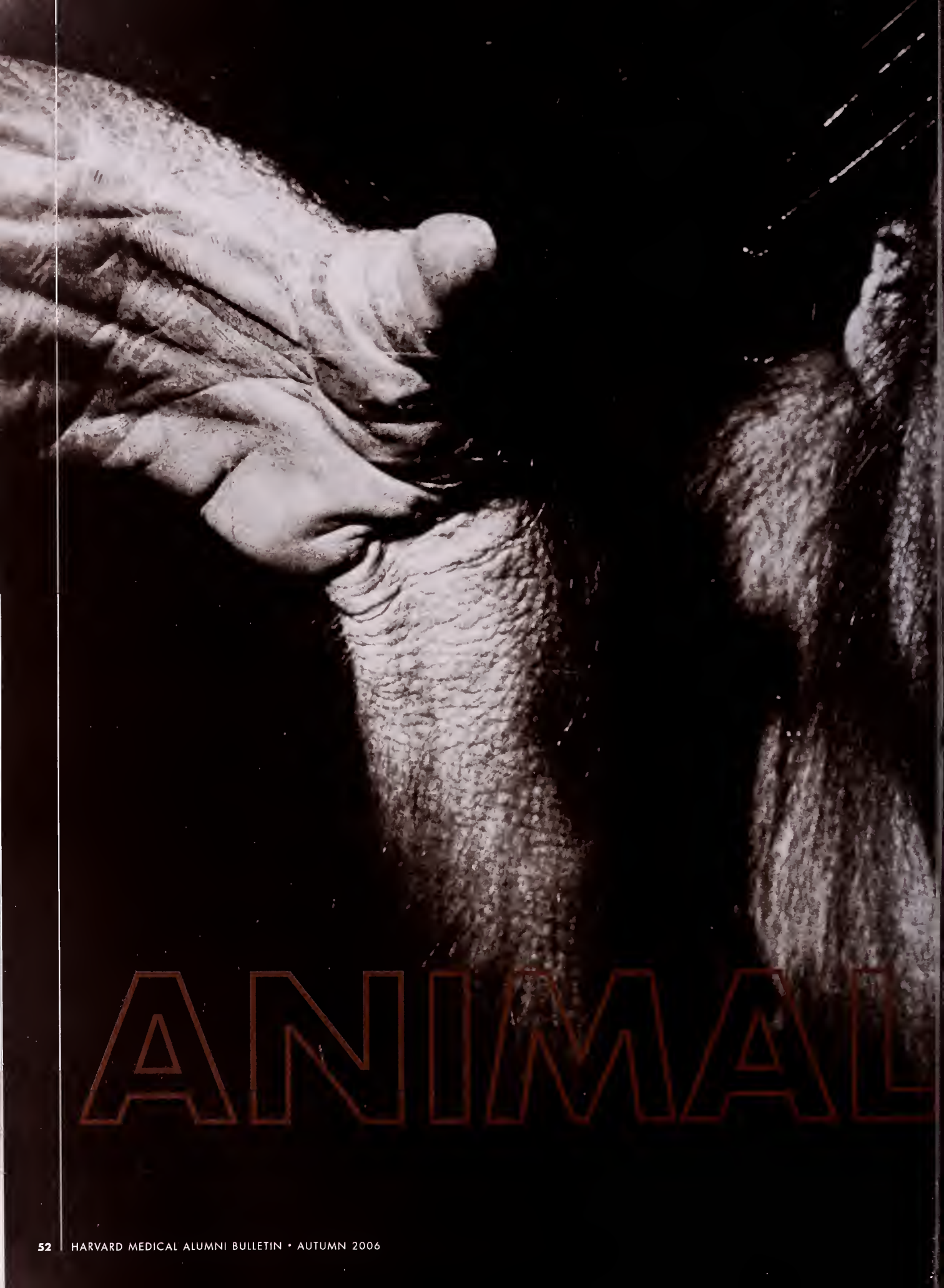
Still thinking magically, I felt certain it was my peering into the darkness that made the bus finally materialize out of the fog. I climbed aboard, joining six other people. I had been the last to be picked up, and we were now being delivered to one treatment building after another: chemotherapy, radiation, different forms of surgery. It felt like an unusual mall, with the shuttle bus transporting us to shops not of our choosing.

Finally, the only other remaining passengers were a couple who appeared to be in their early thirties. Their presence seemed unfair—cancer too early in life. As they clung to each other, I couldn't tell which was the patient. Attempting clinical detachment, I wondered, was it she? Or was it he? They got off, both of them tearful and gripping hands with a desperation that suggested one of them might blow away that very day.

As I watched them, my detachment suddenly crumbled. I realized I had been asking the wrong question. They were *both* the patient; cancer is a family diagnosis. As Charmaine and I had, they had made this frightening but still hopeful journey to a mecca of healing. ■

Ray Babineau '63 is a clinical professor of psychiatry at the University of Rochester School of Medicine in Rochester, New York. After undergoing an operation free of complications, he went on to have radiation treatment, an experience he recounted in the Winter 2003 issue of the Bulletin. *He has been cancer free for five years.*

PHOTO GARY GNIDOVIC/VEER

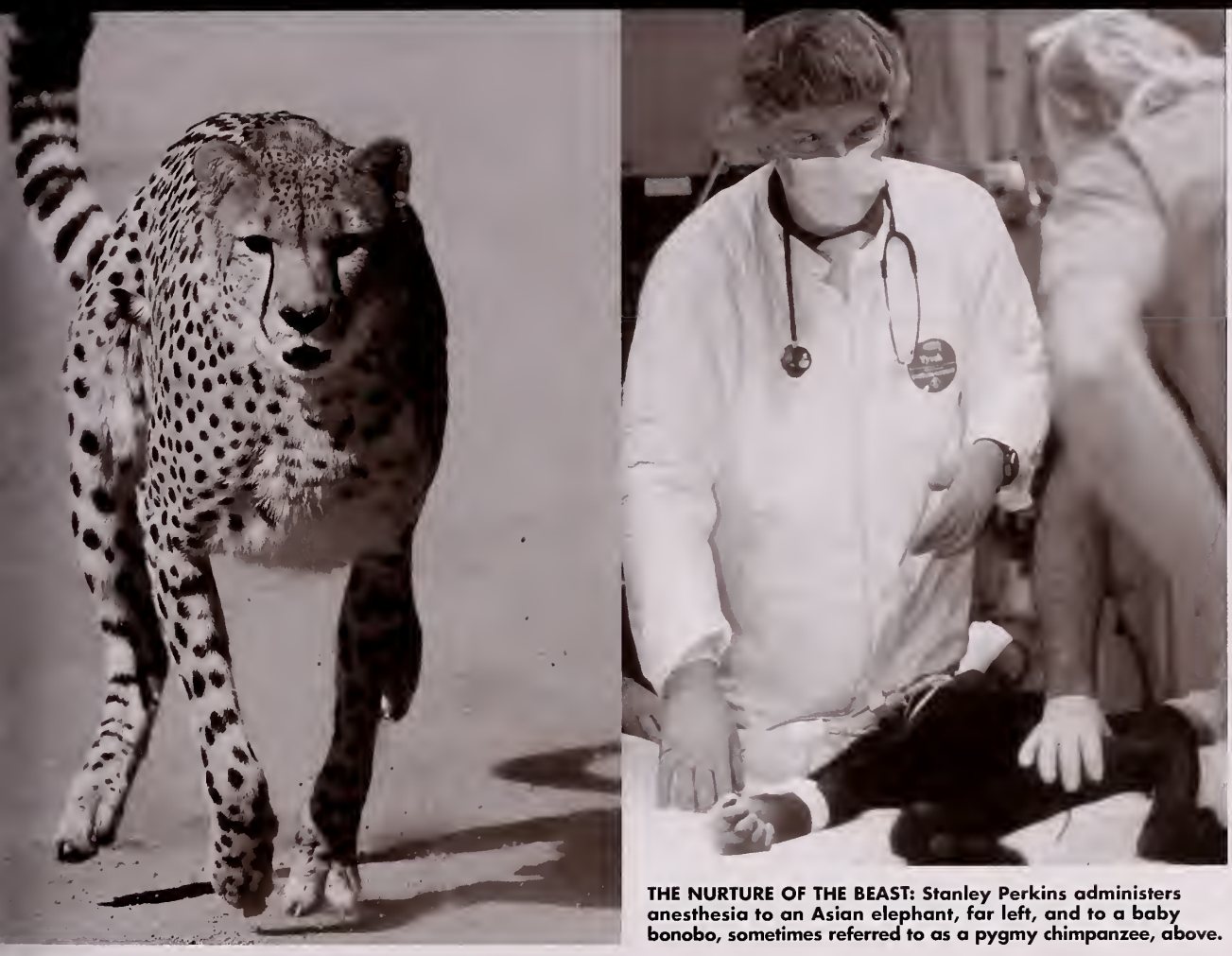

ANIMAL

RITES

Some patients are wilder than others. *by* STANLEY PERKINS

PHOTO ON PREVIOUS SPREAD: DOMINIC DIBBS/PHOTONICA/GETTY IMAGES. ALL OTHER PHOTOS: COURTESY OF THE SAN DIEGO ZOO AND WILD ANIMAL PARK.

IT HAD ALL THE ELEMENTS OF A HORROR FLICK: A GURNEY, TWO UNSUSPECTING doctors, a violent yet sedated patient. In dim light the gurney glides onto a freight elevator, a dull clang reverberating as the wheels bump across the threshold. Slack-faced, with gazes riveted upward, the men watch the lighted arrow make its slow arc. Suddenly, a huge hairy hand springs up, seizing one of the men by the wrist. His eyes wide with panic, the doctor struggles to free himself while the elevator lumbers on, slowly carrying the men and their charge out of sight. As every fan of horror knows, such a scene never bodes well for the doctor. ▫ This time, though, the scene was real; I was the doctor and my patient was one ornery orangutan. In the two decades I've volunteered at the San Diego Zoo and Wild Animal Park as a veterinary anesthesiologist, that tussle with Otis was the closest I've come to being the guy who, when the elevator door opens, is sprawled lifeless on the floor.



THE NURTURE OF THE BEAST: Stanley Perkins administers anesthesia to an Asian elephant, far left, and to a baby bonobo, sometimes referred to as a pygmy chimpanzee, above.

Otis was one of two male orangutans at the zoo. The other, Ken Allen, had earned acclaim as an escape artist. Whenever he grew bored, he would set about loosening the bolts of his cage. A quick slip through the door, a scamper up an incline, and a swing over a wall, and Ken Allen would be out, strolling amid a crowd of people, as if he were just another zoo patron. Each time his keepers discovered one of his escape routes they closed it off, but he would devise a new one. He never seemed to mind being led back into his enclosure, though; he simply relished the challenge of finding new flight paths.

Otis had none of Ken Allen's geniality. He was a bundle of hirsute hostility, and he detested veterinarians—and anyone associated with them—most of all. With the highest strength-to-weight ratio of any primate, orangutans are not to be trifled with, especially when they have Otis's disposition. Whenever I received a call from the zoo about an animal in distress, I would jump into my car and head right over. If that call was about Otis, though, I had to fight the urge to jump into my car and head home instead.

On the day he grabbed me, Otis was scheduled for cosmetic surgery: He needed a wart removed from his nose. But at the zoo even the simplest examinations require sedation. Jeff Zuba, the veterinary intern, tranquilized Otis with a dart so we could transport him to the veterinary hospital. I administered the anesthetic while the veterinarians removed the wart, conducted a physical exam, and untangled his long locks.

During the return trip, I administered the last of the anesthetic. Since we were only minutes from Otis's enclosure I figured we'd be fine. Unfortunately, I had forgotten the sluggishness of the freight elevator that led down to his cage.

Jeff and I were crammed into the tiny elevator with our bodies pressed against the gurney. I was holding the oxygen mask over Otis's face when suddenly I felt his prehensile grip. Now gasping for breath myself, I peeled his leathery digits one by one from my wrist and struggled to reinstate his oxygen mask. When the elevator door finally banged open, Jeff and I sprinted the gurney back to Otis's cage. By the time we had settled the orangutan in his bedroom, he was fully awake and spitting mad. Jeff later confessed the escape plan he had formulated as soon as Otis grabbed my wrist: He would dive under the gurney—and leave me to my own devices.

The Wild Bunch

It was one of my human anesthesia patients who introduced me to the San Diego Zoo. During the preoperative visit, she mentioned her work as a zookeeper. I told her I had always loved animals, and she offered to take me on a behind-the-scenes tour of the zoo. After her recovery she made good on that offer and introduced me not only to her favorite animals, but also to one of the veterinarians. When I asked how anesthetic practices differed for animals, he suggested I visit the zoo's hospital.

On the appointed day I brought with me a new anesthetic we had begun using at my hospital. The veterinarians watched as I anesthetized one of the many stray chickens that stroll the zoo grounds. The experiment was a success: The chicken quickly dozed off, then just as quickly awakened after a predictable deep sleep. The chicken showed no sign of having been anesthetized.

The veterinarians had all received training in anesthesia, but they now realized how much more advanced the field had become in human medicine. They began asking me to consult on their more unusual or difficult cases, or in cases involving rare or valuable animals. Each time I would bring specialized monitoring equipment to supplement the veterinarians' basic instrumentation. The veterinarians immediately adopted the anesthetic agents and techniques I showed them, and the Zoological Society of San Diego raised money to provide them with advanced monitoring equipment. The zoo's patient mortality rate plummeted.

Since that beginning, I've treated lions, tigers, and bears, as well as elephants, rhinos, zebras, and many other exotic species. Cheetahs are among my favorites. These beautiful felines are like oversized, slightly psychotic house cats. It's as if you had a hundred-pound Siamese cozying up to you, purring, licking your hand—and delivering an occasional swat.

Each species—and each procedure—offers its own challenges. Ungulates, for example, are exquisitely sensitive to such narcotics as morphine and fentanyl. The animals simply lose their stimulation to breathe. That vulnerability did, in fact, contribute to one loss: A giraffe's surgery proceeded smoothly, but later, when extubated, the animal simply stopped breathing.

Giraffes pose difficulties for other reasons. When we administer anesthesia, the giraffe's elongated neck becomes floppy, so we have to strap it to a board or risk injuring vertebrae. The giraffe's long and narrow jaw makes it impossible to intubate using a laryngoscope, so we do the intubations blind, with an ear at one end of the tube monitoring the breath sounds as we advance the tube toward the larynx.

Sleeping Giants

The most technically complex animal I've anesthetized, though, is the elephant. The sheer weight of an anesthetized elephant lying on its side can cut blood flow to the muscles and compromise the animal's breathing, so we have to enrich the air supply with oxygen—and the surgeons have to be quick. But elephant breaths are like small windstorms. Having them depend on too small a ventilator tube would be like asking a human to breathe through a straw all day long.

To allow the elephant to breathe as naturally as possible while enriching the air with as much oxygen as we can, we constructed a rebreathing apparatus from an ordinary dryer exhaust hose, some large plastic bags, and a couple of oxygen tanks. Using this contraption, we inserted the elephant's trunk into the end of the dryer hose and performed what we believe was the first successful Caesarean section on an elephant.

Raised in captivity, the elephant—Jean—likely did not realize she was pregnant. Since an elephant in labor can stop her contractions at will, we assume Jean, confused by the pains, stopped the labor and never restarted it. The fetus died in utero, and the decaying tissue was making Jean ill. We performed a complicated Caesarean to remove the fetus.

My experience in anesthetizing elephants was put to ecological use more recently, when Jeff—my fellow Otis survivor and now a veterinarian at the Wild Animal Park—asked me to consult on an elephant population control project in southern Africa. Conservation efforts have been so effective in some of the region's national parks and land reserves that many have become overpopulated with elephants, threatening biodiversity, habitat, and the success of other species. One park alone has 7,000 more elephants than the land can support.

A team of veterinarians and conservationists has concluded that the most humane and effective approach for controlling the population is to reduce the birth rate by performing laparoscopic vasectomies on the older dominant males. We knew the anesthetic procedure had to be safe, reliable, and simple enough for the conservationists to do by themselves, with minimal equipment. Earlier this year, then, Jeff and I designed a portable breathing system. The resultant apparatus—a modification of the system we used for Jean—is an enormous endotracheal tube attached to an assemblage of large tubes, one-way valves, and oxygen ports. This system has since been used on multiple elephants in the field, without failure.

The Wild Zoo Yonder

As a research facility that works with so many exotic animals, the medical center at the San Diego Wild Animal Park receives requests for assistance from all over the world. One day the call came from Anchorage: One of the elephants at the Alaska Zoo, Annabelle, needed a tooth extracted. The zoo had originally been built around Annabelle, when a local grocer won her in a national contest but had no place to house her. So when the veterinarian, veterinary dentist, and I all flew north to care for her, we became instant heroes.

INTO THE STRETCH: Stanley Perkins, top left, administers anesthesia to a giraffe. These animals, with their attenuated necks and long and narrow jaws, pose special challenges for anesthesiologists.

The most memorable of the many trips I've since made to the Alaska Zoo, though, involved another dental problem. Binky, one of two polar bears there at the time, needed a root canal. He had been taken to the zoo as an orphaned cub found wandering the Alaskan Arctic, and now as an adult he was frustrated with his concrete-and-steel home. In his efforts to chew to freedom he had broken three of his canine teeth.

Binky was the first bear I had ever been asked to anesthetize, and I felt nervous. We tranquilized him, then dragged all 850 pounds of bear from his bedroom to his exhibition area to ensure adequate workspace. I was using a lighted laryngoscope in my effort to insert a one-inch-wide endotracheal tube. But the day was bright, his trachea was deep, and his tongue was flopping all around, so I couldn't see well enough to guide the tube.

"Just reach in there," said Jim Oosterhuis, the head veterinarian from San Diego, "and feel for his larynx."

"You want me"—here I paused to stare at Jim—"to put my arm down the throat of a just slightly sedated polar bear?"

"Sure!" Jim said. "You'll have no problem at all."

I had—until that moment, at least—trusted Jim implicitly. Drawing on that now shaky trust, I took a deep breath and plunged a hand down Binky's throat, pressing deeper until I could feel the tip of his epiglottis. With my other arm, I guided the tube down his trachea. Just then I noticed that polar bear teeth—the sharpest of all ursine teeth—were resting inches below my shoulder. If that tranquilizer suddenly wears off, I thought, they're going to start calling me Lefty.

But the maneuver worked, and Binky recovered well enough to gain international attention—even cult hero status—some years later for that very set of teeth. The catalyst was an Australian tourist who decided to scramble over two safety rails to get a good photo of him. Binky obligingly poked his head through the bars, but then wrapped his jaws around her leg. After a brief skirmish, he settled for her red-and-white sneaker. The tourist escaped with a broken leg, bite wounds, and a reputation for dimwittedness.

Animal Magnetism

When I describe my work at the San Diego Zoo and Wild Animal Park, people ask why I didn't go into veterinary medicine. I had considered doing so, but then realized I would find it emotionally draining to deal with suffering animals that couldn't understand what was happening to them. Now, by combining my vocation with my avocation, I'm able to enjoy the rewards of bringing the latest advances in human medicine to the veterinary world.

My volunteer work with animals has given me perspective on my work with humans. Starting intravenous lines on people now seems easy after having started them on powerful and struggling gorillas. Similarly, after intubating four-ton elephants, I no longer feel as anxious when morbidly obese patients come to my operating room. I also appreciate being able to explain to my patients what I'm doing—and to hear their thanks.

And, best of all, sharing elevators with human patients on gurneys has always been blessedly uneventful. ■

Stanley Perkins '80 is an anesthesiologist at the Sharp Memorial Hospital in San Diego, where he cares for a variety of humans. When he's not putting people—or animals—to sleep, he's flying his Turbo Commander with his dog, Amy, in the co-pilot's seat.

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